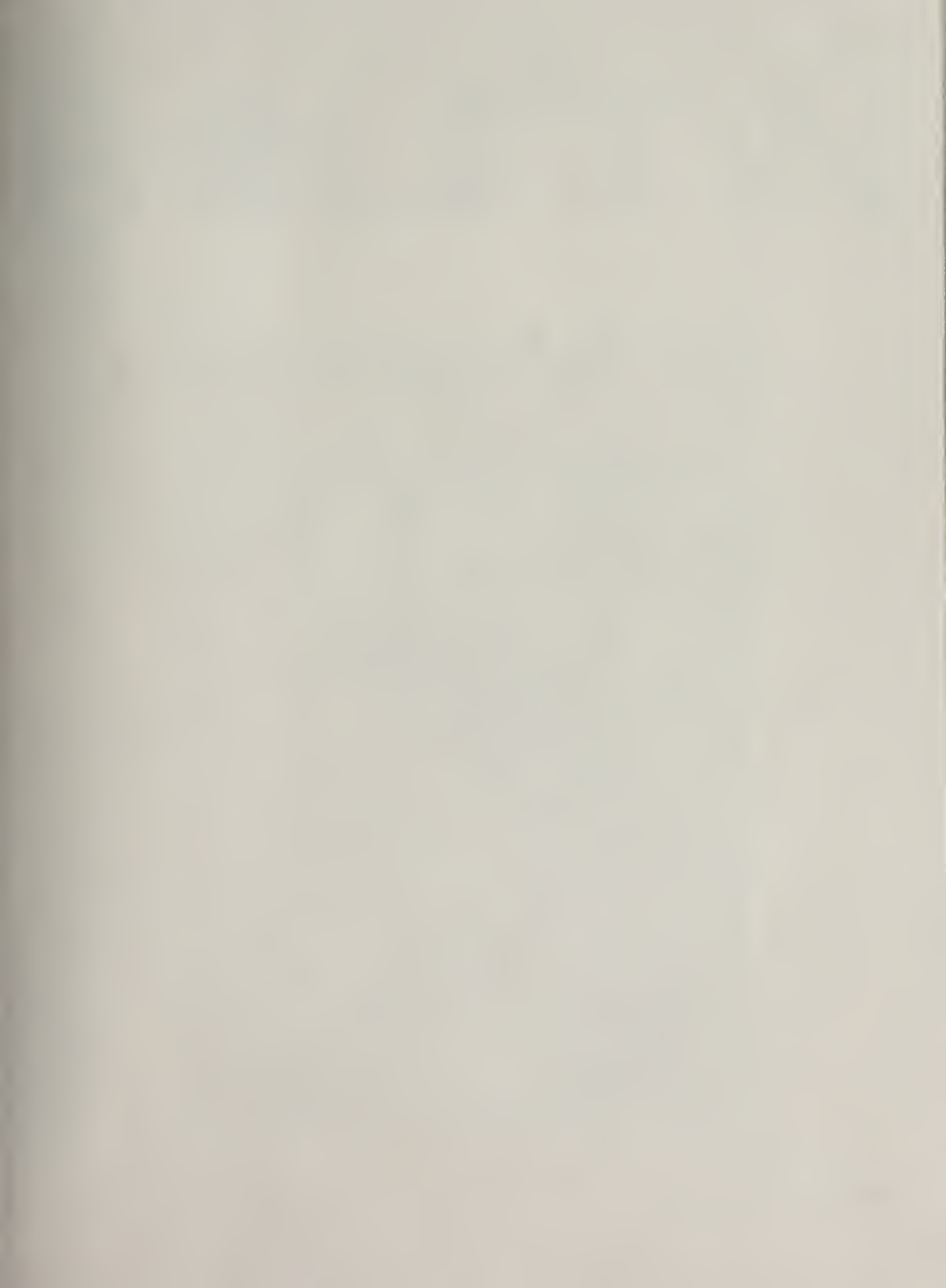
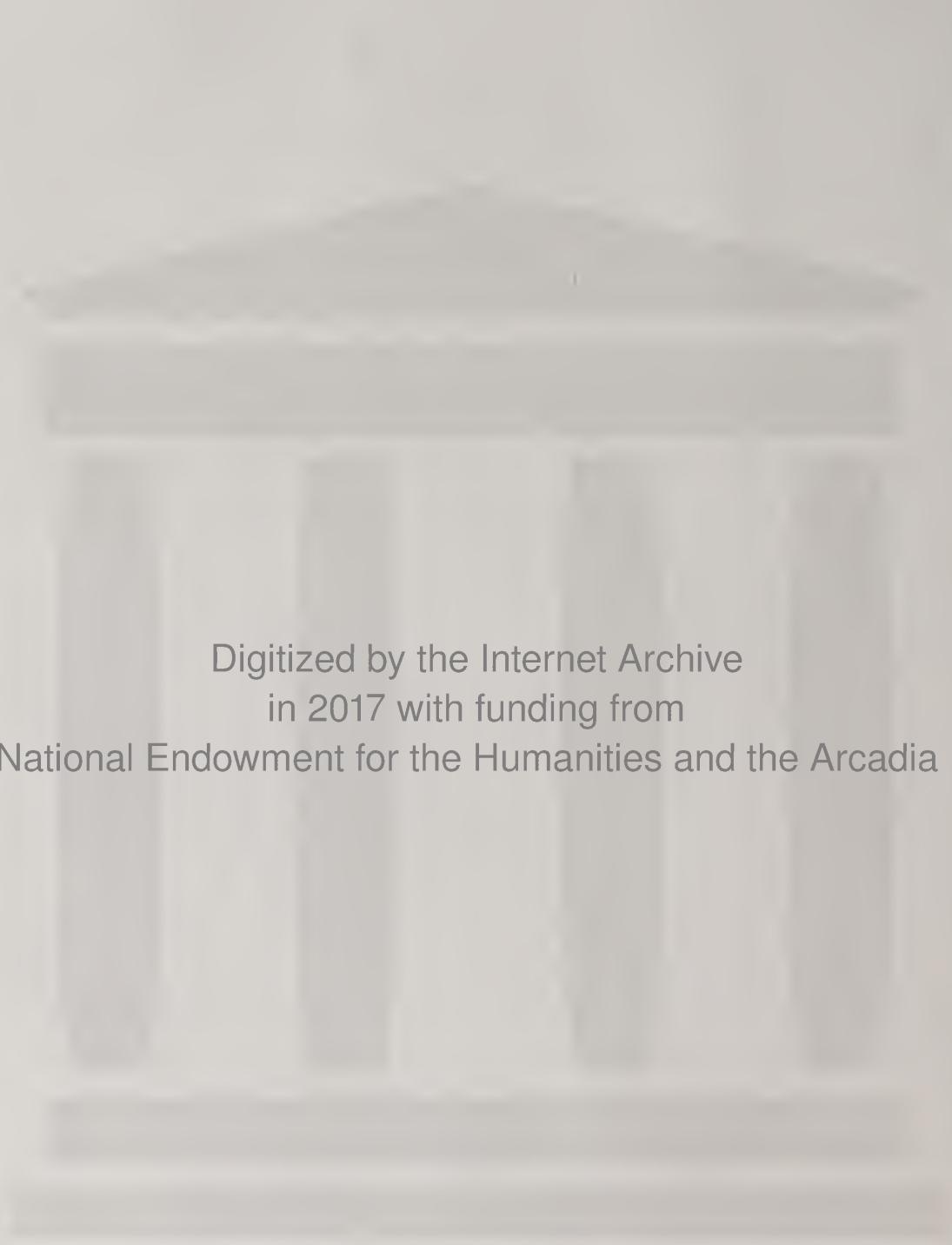




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ASOCIACION MEDICA DE PUERTO RICO

# B LETIN


BOLETIN DE LA ASOCIACION DE PUERTO RICO



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**"YES, THERE IS  
LIFE AFTER  
BREAST CANCER.  
AND THAT'S THE  
WHOLE POINT."**

—Ann Jillian



A lot of women are so afraid of breast cancer they don't want to hear about it.

And that's what frightens me.

Because those women won't practice breast self-examination regularly.

Those women, particularly those over 35, won't ask their doctor about a mammogram.

Yet that's what's required for breast cancer to be detected early. When the cure rate is 90%. And when there's a good chance it won't involve the loss of a breast.

But no matter what it involves, take it from someone who's been through it all.

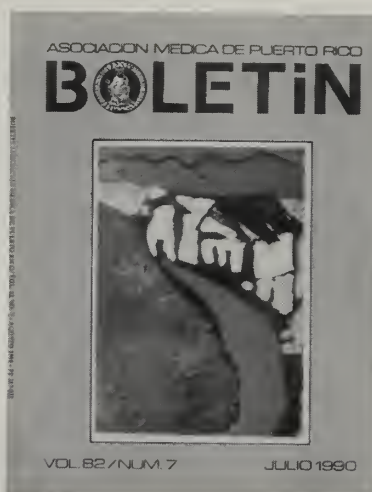
Life is just too wonderful to give up on. And, as I found out, you don't have to give up on any of it. Not work, not play, not even romance.

Oh, there is one thing, though.

You do have to give up being afraid to take care of yourself.



Get a checkup. Life is worth it.



## *Nuestra Portada*

**El Camino de la Casa de los Poetas.** Obra del artista puertorriqueño Pablo Romero. El autor es natural de Santurce, Puerto Rico y sus obras pictóricas figuran en numerosas colecciones. Entre las más conocidas están el Museo Metropolitano de Nueva York, Museo del Bronx, el Ateneo Puertorriqueño y el Museo del Barrio en Nueva York. Recientemente sus obras fueron expuestas en la Sexta Bienal del Retrato Contemporáneo en Tuzla, Yugoslavia.

La obra de la portada es parte de una serie titulada La Casa de los Poetas. Esta serie representa al quehacer creativo de cada individuo visto desde su propio mundo (su casa) y el proceso de crecimiento de cada persona.

El Camino de la Casa de los Poetas pertenece a la colección privada del Dr. Manuel R. Pérez-González, Radiólogo que ejerce en Santurce. La Junta Editora del Boletín de la Asociación Médica de Puerto Rico le agradece al Dr. Pérez-González su colaboración con nuestra revista.

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# CLINICAL STUDIES

## Treatment of Psoriasis with Triamcinolone Acetonide 0.1% Under Occlusion: A Comparison of Two Hydrocolloid Dressings

José R. González, MD  
Francis Cabán, MD

**Abstract:** A clinical, randomized, parallel study was undertaken to compare the efficacy of a widely known steroid preparation, triamcinolone acetonide 0.1% cream, in occlusion with two different hydrocolloid dressings, namely Duoderm® and Actiderm®, in the treatment of chronic plaques of psoriasis. A total of 23 patients with psoriasis were entered in the study. Two similar psoriatic plaques were identified in each patient, triamcinolone acetonide cream was applied, and a randomized table assigned the sides of the body to which each dressing was to be used for each patient. Changing of the dressing, with reapplication of the cream was done every 48 hours on each side until the lesions cleared or for a maximum of three weeks.

At the end of the three weeks-therapy, period, 12 lesions had totally cleared with Duoderm and 13 with Actiderm. Seven lesions had achieved either marked or moderate improvement with duoderm and the same results were observed with Actiderm. Only three of 22 had mild improvement with Duoderm and two of 22 with Actiderm. No side effect were noted and none of the patients became worse during this treatment.

This study demonstrated the beneficial effects of triamcinolone acetonide 0.1% cream under occlusion with two different hydrocolloid dressings in the treatment of chronic resistant plaques of psoriasis. The use of a hydrocolloid dressing in combination with steroid adds another therapeutic option for the treatment of chronic localized psoriatic lesions.

Occlusive dressing therapies have received particular attention in the past few years and positive effects in a variety of skin diseases have been attributed to them. These diseases range from pressure sores and chronic leg ulcers to epidermolysis bullosa.<sup>1-3</sup> Several studies have shown better cosmetic results when these dressings have been used on surgical wounds.<sup>4-5</sup> Eaglestein,<sup>6</sup> recently reviewed the clinical experiences with occlusive therapy in the treatment of leg ulcers.

The occlusive agents have been divided into those which are permeable to oxygen and those which are not, however, all are designed to maintain the hydration of tissues. Permeable dressings include biocclusive, opsite and tegaderm; the non-permeable include hydrocolloid dressings such as Duoderm® and A-117 (Actiderm®).

Winter,<sup>7</sup> in 1962, first documented the enhancing properties of the occlusive dressing on the rate of re-epithelialization. The acceleration of wound healing has been explained primarily as a function of unobstructed migration of epidermal cells in a moist environment on the wound surface, rather than the effects on mitosis of epidermal cells. Both, oxygen permeable and oxygen impermeable dressings have been found to speed epidermal re-epithelialization by about 40%. Hydrocolloid dressings have been found to promote a faster rate of healing compared with polyurethane film and gauze in wet to dry dressings.<sup>5</sup>

Other properties attributed to occlusive dressings have included: increased skin penetration, increased absorption of applied substances, prevention of bacterial invasion in wounds, increase in collagen synthesis<sup>6</sup> improved cosmetic results of surgical wounds,<sup>4-5</sup> relief of pain from skin ulceration<sup>2</sup> and equilibration of pH of occluded tissue with the interstitial fluid.

The hydrocolloid dressings are composed of pectin, gelatin, carboxymethyl cellulose and sodium polysobutylene.

The adhesive properties of Duoderm, as well as Actiderm, are specially designed for improved adherence to skin contours. However, Actiderm is thinner than Duoderm and thus is easier to contour to the skin.

The use of topical steroids under occlusion is commonly accepted as one form of enhancing the delivery and penetration of a given steroid. We are unaware of published studies of the use of steroids under hydrocolloid dressings in the treatment of chronic plaque psoriasis.

The purpose of this study was to compare the efficacy of a currently, widely used steroid cream, triamcinolone acetonide (Kenalog®) 0.1% in occlusion, with Duoderm vs. 117A (Actiderm) to demonstrate if the use of these dressings may speed resolution of chronic psoriatic lesions. A total of twenty-three patients with chronic



psoriasis were entered in the study, for each patient a psoriatic lesion on the body side was treated with triamcinolone acetonide cream 0.1% under occlusion with Duoderm, while a similar lesion on the contralateral side was treated with triamcinolone cream 0.1% and 177-A (Actiderm) occlusive dressing.

### Patients and Methods

Twenty-four volunteers from the University of Puerto Rico Dermatology Clinics with chronic psoriasis vulgaris with bilateral distribution were asked to participate in the present study. Patients younger than 14 years of age and pregnant females were excluded. After informed consent was obtained, medical history on disease course, previous therapies, allergies and family history was obtained. Previous therapies were discontinued for at least four weeks prior to the clinical trials.

Two similar symmetrical psoriatic plaques were identified for each patient. Lesions were cleaned with a mild soap and water and then carefully dried. Triamcinolone acetonide 0.1% cream was applied leaving a thin coating of the cream on the lesions. A randomized table assigned the side of the body to which each dressing was to be used for each patient. To insure good adhesion the dressings size was cut and extended 1.5cm beyond the margin of the lesions. Fig. 1



Figure 1. Method of application of occlusive dressing, a 1.5 cm margin is left to insure good adhesion.

Patients were instructed to leave the dressings on for 48 hours at the end of which time, they were told to wash the lesions with a mild soap and water, apply the triamcinolone 0.1% cream and apply the dressings to each side as assigned. This procedure was repeated on each side until the lesions cleared or for a maximum of three weeks.

The patients were then asked to come in four, weekly follow-up visits in which grading of the lesions and photographs were obtained. Side effects were also recorded in each visit, as well as compliance with this treatment including acceptance or possible problems derived from the application of the dressings. All patients were seen a week after completing the protocol including those with early clearance, drop outs and those who completed the three-week course.

### Results

Twenty four patients were entered in this study, two were excluded for not complying with the protocol. Sex distribution consisted of 14 males and 8 females. The age ranged from 14 to 76 years with an average age of 49 years. Twenty patients had had the disease for more than two years, only in two instances was the disease present for less than one year.

Pretreatment clinical evaluations revealed that four patients had skin lesions graded as mild, seventeen had moderate disease and one had severe thick scaly plaques. Fig. 2



Figure 2. Patient #5 photograph of Rt arm at pretreatment visit. Note thick scaling and infiltrated plaques.

The overall evaluation of therapeutic response to therapy went as follows: at week 1, five lesions treated with Duoderm dressing had complete clearing vs none with Actiderm; four patients using Duoderm vs 16 with Actiderm had moderate improvement and five had a mild response with each dressing. One patient had no clinical response with either dressing.

At week 2 seven lesions had a complete clearing with Duoderm vs. six with the Actiderm. Eleven had moderate



improvement with Duoderm while 13 with Actiderm showed the same grading. Three lesions had a mild response with each dressing. One lesions treated with Duoderm showed no response.

At the end of the 3-week therapy period, 12 lesions had totally cleared with Duoderm vs. 13 with Actiderm. Fig. 3. Seven lesions had achieved either marked or moderate improvement with Duoderm while another seven lesions showed the same response with Actiderm. Three lesions vs. two had a mild response with Duoderm vs. Actiderm respectively, see Table I.



Figure 3. Patient #5 at the end of 3-week treatment trial. Marked resolution of the scaling and the infiltration of the plaques.

Table I

Overall Evaluation of Therapeutic Response to Therapy

	Duoderm	177A
Complete Clearing	12	13
Marked Improvement	5	3
Moderate Improvement	2	4
Mild Improvement	3	2
No Response	-	-
Worse	-	-

Patients were evaluated a week after having concluded the treatment period. No additional treatment was used during this period of time. All patients had maintained the same level of clinical improvement observed at week three except for patient number 6 whose clinical response with both dressings response down-graded to moderate improvement (complete clearance at week 3) and patient number 9 who relapsed to the initial degree of severity (mild improvement) with both dressings. These results are summarized in Table II.

Side Effects and Patient Acceptability: None of the patients reported any significant adverse effects and none were observed by the investigators during the clinical evaluations. Three patients complained of mild discomfort when changing dressings both (Duoderm and Actiderm) on hairy areas due to hair pulling, but such discomfort could be reasonably tolerated and did not

Table II

Patient Description and Results

Pt	Sex	Age	Visit 1	Visit 4		Visit 5	
				D	A	D	A
1	F	31	Mod.	3	3	3	3
2	M	64	Mod.	3	3	3	3
3	F	76	Mild	2	2	3	3
4	M	54	Mod.	1	2	1	2
5	M	33	Mod.	2	2	2	2
6	M	49	Mod.	3	3	2	2
7	F	66	Mod.	3	3	3	3
8	M	66	Marked	With Drawn			
9	M	52	Mild	1	1	0	0
10	F	44	Mod.	2	2	2	0
11	M	49	Mod.	2	2	2	2
12	M	43	Mod.	2	3	3	3
13	M	41	Mod.	1	1	1	1
14	F	63	Mod.	3	3	3	3
15	M	65	Mod.	3	3	3	3
16	M	77	Mod.	2	2	2	2
17	M	50	Marked	3	3	3	3
18	F	30	Mod.	3	3	3	3
19	F	41	Mild	3	3	3	3
20	F	61	Mild	2	3	2	3
21	M	67	Mod.	2	2	2	2
22	M	12	Mod.	3	3	3	3
23	F	14	Mod.	3	3	3	3

0 ± No change 1 ± Mild Improvement

2 = Moderate or Marked Improvement 3 = Complete Clearance

warrant discontinuation of treatment. Good adherence was obtained in hairy areas but patients were encouraged to shave the surrounding skin if possible.

No side effects such as the Koebner phenomenon, contact dermatitis, maceration, folliculitis or other infections were found at the treated sites.

Most of the patients found both dressings excellent (17 patients) or good modalities of treatment. Only one patient judged the acceptance as fair. All agreed that the treatment regimen was an easy one to comply with.

## Discussion

The results of this study demonstrate the beneficial effects of using triamcinolone acetonide 0.1% cream in occlusion with hydrocolloid dressings in chronic psoriatic lesions previously resistant to other forms of therapy including topical steroids without occlusion. Our study showed that the majority of patients achieved a complete clearing, 11 using Duoderm and 13 using Actiderm at the end of the 3-week trial, in fact most of the lesions in this category obtained a complete remission within the first 2 weeks of undergoing the occlusive treatment. Almost one third of the patients, 31.8% were able to show considerable improvement with marked flattening of the plaques, and absence of pruritus and scaling. This group was classified as either marked or moderate improvement and again no significant difference would be observed between Duoderm or Actiderm in either the total number of patients or lesions attaining this grading or improvement.

Only a small number of patients obtained a mild response, 3/22 for Duoderm and 2/22 Actiderm. Worsening of the psoriatic plaques, adverse effects or

lack of compliance was not observed in any of the patients.

Recently, Friedman<sup>10</sup> prompted by Shore's findings<sup>11</sup> that Band Aid occlusion improved psoriatic plaques, demonstrated positive results using Hydrocolloid Dressings alone for the treatment of chronic psoriatic plaques. In his study 16 out of 34 (47%) psoriatic plaques cleared and another 14 had some improvement; however the number of weeks in occlusive dressing therapy was longer than ours.

The mechanism responsible for the efficacy of triamcinolone acetonide 0.1% cream under hydrocolloid occlusion is probably the result of a combination of two factors. First the improved topical steroid absorption under occlusion which has been found to increase approximately 100 times, and secondly the effect of prolonged occlusion. The latter has been shown to decrease mitotic rate<sup>12</sup> inhibit the development of parakeratosis,<sup>13</sup> restore the granular cell layer<sup>14</sup> and diminishes the ionic bonding forces between corneocytes which enhances desquamation.<sup>13</sup> The rapid response of some lesions which had cleared by one week of therapy in our study speaks in favor of a synergism between these two factors.

A regression of the clinical improvement to the pre treatment stage was observed in two patients, seven days after discontinuing the dressing therapy. This regression can reasonably be expected if therapy is discontinued abruptly on lesions which have shown recent improvement. In contrast to these two patients, we have followed up three patients without any form of therapy for more than six months and the previously treated areas have maintained a complete regression. The factors which have influenced this excellent response are unknown.

Three patients complained of mild discomfort secondary to hair pulling when removing the dressings, but side effects such as Koebner phenomenon contact dermatitis or steroid related effects (skin atrophy, telangiectasias, hypopigmentation, etc.) were not reported. In Friedman's study,<sup>10</sup> four patients developed a Koebner phenomenon restricted to the tested sites. The lack of this adverse effect in our study is probably due to the fact that in our patients a cream was applied between the skin and the dressing reducing in this way the adherence between the two.

The ideal time to change the dressing has not been determined but probably is between 2-7 days given difference in adhesiveness at different body sites. Dense hairy regions may need to be changed every 48 hours compared to now glabrous skin which could hold the dressing for several days.

In terms of the clinical parameters evaluated, pruritus and the scaling of the lesions in most cases resolved by the first or second week of therapy for both dressings. The erythema and infiltration showed a slower but steady improvement reaching resolution or marked improvement in most cases.

In conclusion, this study has demonstrated the beneficial effects of triamcinolone 0.1% cream under occlusion with to different hydrocolloid dressings in the treatment of psoriasis. Both dressings studied, Actiderm and Duoderm showed to be very efficacious and no signifi-

cant differences in adherence, side effects or clinical response were found. The use of topical steroids under hydrocolloid dressings adds another therapeutic option for the treatment of chronic localized psoriatic lesions.

**Resumen:** Se reporta un estudio clínico paralelo, y al azar, donde se compara la efectividad de acetona de triamcinolona 0.1% en crema, en oclusión con dos vendajes hidrocoloidales, Duoderm® y Actiderm® en el tratamiento de lesiones crónicas de psoriasis. Se seleccionaron lesiones simétricas en 23 pacientes a los cuales se le aplicó la crema de triamcinolona ocluida por el vendaje. Este proceso se repetía cada 48 horas hasta que desaparecieran las lesiones o por un máximo de tres semanas.

Al finalizar las tres semanas, 12 lesiones ocluidas con Duoderm vs. 13 ocluidas con Actiderm aclararon totalmente. Siete lesiones alcanzaron una mejoría marcada o moderada con Duoderm y resultados idénticos en esta categoría se observaron con Actiderm. Solamente tres de 22 lesiones mostraron una mejoría leve con Duoderm y dos de 22 con Actiderm. No se reportaron efectos colaterales ni empeoramiento de lesiones.

Este estudio demostró los efectos beneficiosos del régimen oclusivo de vendajes hidrocoloidales en combinación con crema esteroidales en el manejo de lesiones crónicas de psoriasis en placa localizadas.

El uso de vendajes hidrocoloidales en combinación con crema corticoesteroidales es una opción nueva para el tratamiento de psoriasis crónica localizada.

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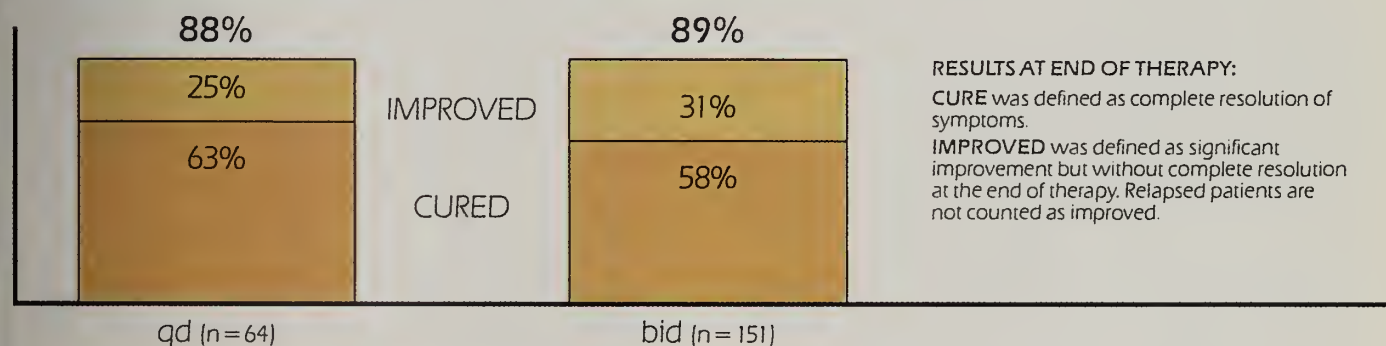
# THE FIRST ORAL THIRD GENERATION CEPHALOSPORIN FOR OTITIS MEDIA\*

Once-Daily Dosing Maintains Inhibitory Drug Concentrations Against Important Pathogens in Otitis Media

SUPRAX Oral Suspension Provides Outstanding Clinical and Bacteriologic Success in Otitis Media<sup>4,5</sup>

Excellent Clinical Success in Otitis Media<sup>†</sup>

191 of 215 Patients Effectively Treated qd or bid With 10-Day Course of SUPRAX Oral Suspension<sup>‡</sup>



The Only Cephalosporin Indicated for  $\beta$ -Lactamase Producing Strains of Haemophilus influenzae and Branhamella catarrhalis

The Only Once-a-Day for Otitis Media

Convenient Dosing and Flexibility

- 8 mg/kg per day in children regardless of severity of infection
- Administered once or twice daily with or without food

\* Due to susceptible organisms. Please consult **Clinical Studies** section of brief summary for limitations on usage.

† Results of clinical trials in infections due to *Haemophilus influenzae*, *Branhamella catarrhalis*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae*. Please consult **Clinical Studies** section of brief summary for limitations on usage.

‡ Tablets should not be substituted for suspension in otitis media.

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**BRIEF SUMMARY.** Please see package insert for full Prescribing Information  
**INDICATIONS AND USAGE**

Otitis Media caused by *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Moraxella (Branhamella) catarrhalis*, (most of which are beta-lactamase positive), and *Streptococcus pyogenes*.

**Note:** For information on otitis media caused by *Streptococcus pneumoniae*, see **CLINICAL STUDIES** section.

**Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis** caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* (beta-lactamase positive and negative strains).

Perform culture and susceptibility studies to determine causative organism and its susceptibility to SUPRAX. Therapy may begin while waiting for study results and may be adjusted when results are known.

**Pharyngitis and Tonsillitis** caused by *Streptococcus pyogenes*.

**Note:** Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* infections, including the prophylaxis of rheumatic fever. SUPRAX is generally effective in the eradication of *S. pyogenes* from the nasopharynx; however, data establishing the efficacy of SUPRAX in the subsequent prevention of rheumatic fever are not available.

**Uncomplicated Urinary Tract Infections** caused by *Escherichia coli* and *Proteus mirabilis*.

\*Efficacy for this organism was studied in fewer than ten patients with otitis media.

**CLINICAL STUDIES**

In clinical trials of otitis media in nearly 400 children between the ages of 6 months to 10 years, *Streptococcus pneumoniae* was isolated from 47% of the patients, *Haemophilus influenzae* from 34%, *Moraxella (Branhamella) catarrhalis* from 15%, and *Streptococcus pyogenes* from 4%.

The overall response rate of *Streptococcus pneumoniae* to cefixime was approximately 10% lower and that of *Haemophilus influenzae* or *Moraxella (Branhamella) catarrhalis* approximately 7% higher (12% when beta-lactamase positive strains of *H. influenzae* are included) than the response rates of these organisms to the active control drugs.

In these studies, patients were randomized and treated with either cefixime at dose regimens of 4 mg/kg bid or 8 mg/kg qd, or with a standard antibiotic regimen. Sixty-nine to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated two to four weeks posttreatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs (18% including those patients who had *Haemophilus influenzae* resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the two- to four-week follow-up, a total of 30%-31% of patients had evidence of either treatment failure or recurrent disease.

Bacteriological Outcome of Otitis Media at Two- to Four-Weeks Posttherapy  
Based on Repeat Middle Ear Fluid Culture or Extrapolation from Clinical Outcome

Organism	Cefixime <sup>(a)</sup> 4 mg/kg bid	Cefixime <sup>(a)</sup> 8 mg/kg qd	Control <sup>(a)</sup> drugs
<i>Streptococcus pneumoniae</i>	48/70 (69%)	18/22 (82%)	82/100 (82%)
<i>Haemophilus influenzae</i> beta-lactamase negative	24/34 (71%)	13/17 (76%)	23/34 (68%)
<i>Haemophilus influenzae</i> beta-lactamase positive	17/22 (77%)	9/12 (75%)	1/1 <sup>(b)</sup>
<i>Moraxella (Branhamella)</i> <i>catarrhalis</i>	26/31 (84%)	5/5	18/24 (75%)
<i>Streptococcus pyogenes</i>	5/5	3/3	6/7
All Isolates	120/162 (74%)	48/59 (81%)	130/166 (78%)

<sup>(a)</sup> Number eradicated/number isolated

<sup>(b)</sup> An additional 20 beta-lactamase positive strains of *Haemophilus influenzae* were isolated, but were excluded from this analysis because they were resistant to the control antibiotic. In nineteen of these the clinical course could be assessed, and a favorable outcome occurred in 10. When these cases are included in the overall bacteriological evaluation of therapy with the control drugs, 140/185 (76%) of pathogens were considered to be eradicated.

Tablets should not be substituted for suspension when treating otitis media.

**CONTRAINDICATIONS**

Known allergy to cephalosporins

**WARNINGS**

**BEFORE THERAPY WITH SUPRAX IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO SUPRAX OCCURS, DISCONTINUE THE DRUG. SERIOUS, ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.**

Administer cautiously to allergic patients

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of severe antibiotic-associated diarrhea including pseudomembranous colitis. Pseudomembranous colitis has been reported with the use of SUPRAX and other broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins). It is important to consider this diagnosis in patients who develop diarrhea in association with antibiotic use. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment and may range in severity from mild to life threatening. Mild cases usually respond to drug discontinuation alone. Moderate-to-severe cases should be managed with fluid, electrolyte, and protein supplementation. When the colitis is not relieved by drug discontinuation, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be excluded.

**PRECAUTIONS**

**General:** Prolonged use may result in overgrowth of nonsusceptible organisms. If superinfection occurs, take appropriate measures.

Carefully monitor patients on dialysis. Adjust dosage of SUPRAX in patients with renal impairment and those undergoing continuous ambulatory peritoneal dialysis and hemodialysis. (See **DOSAGE AND ADMINISTRATION**.)

Prescribe cautiously in patients with a history of gastrointestinal disease, particularly colitis.

**Drug Interactions:** No significant drug interactions have been reported to date.

**Drug/Laboratory Test Interactions:** A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.

SUPRAX cefixime administration may result in a false-positive reaction for glucose in the urine using Clinistix<sup>®</sup>, Benedict's solution, or Fehling's solution. Use glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix<sup>®</sup> or Tes-Tape<sup>®</sup>).

A false-positive direct Coombs test has been reported during treatment with other cephalosporin antibiotics; therefore, it should be recognized that a positive Coombs test may be due to the drug.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Although no lifetime animal studies have been conducted to evaluate carcinogenic potential, no mutagenic potential of SUPRAX was found in standard laboratory tests. Reproductive studies revealed no fertility impairment in rats at doses up to 125 times the adult therapeutic dose.

**Usage in Pregnancy:** Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of harm to the fetus due to SUPRAX.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Labor and Delivery:** SUPRAX has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

**Nursing Mothers:** It is not known whether SUPRAX is excreted in human milk. Consider discontinuing nursing temporarily during treatment with this drug.

**Pediatric Use:** Safety and effectiveness of SUPRAX in children aged less than 6 months have not been established.

The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension, was comparable to adult patients receiving tablets.

**ADVERSE REACTIONS**

Most adverse reactions observed in clinical trials were of a mild and transient nature. Five percent (5%) of patients in the US trials discontinued therapy because of drug-related adverse reactions. Commonly seen adverse reactions in US trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the bid or the qd regimen. Clinically mild gastrointestinal side effects occurred in 20% of all patients, moderate events occurred in 9% of all patients, and severe adverse reactions occurred in 2% of all patients. Individual event rates included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 4%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to adult patients receiving tablets.

Symptoms usually responded to symptomatic therapy or ceased when SUPRAX was discontinued.

Several patients developed severe diarrhea and/or documented pseudomembranous colitis, and a few required hospitalization.

The following adverse reactions have been reported following the use of SUPRAX. Incidence rates were less than 1 in 50 (less than 2%), except as noted above for gastrointestinal events.

**Gastrointestinal:** Diarrhea, loose stools, abdominal pain, dyspepsia, nausea, and vomiting. Several cases of documented pseudomembranous colitis were identified during the studies. The onset of pseudomembranous colitis symptoms may occur during or after therapy.

**Hypersensitivity Reactions:** Skin rashes, urticaria, drug fever, and pruritus.

**Hepatic:** Transient elevations in SGPT, SGOT, and alkaline phosphatase.

**Renal:** Transient elevations in BUN or creatinine.

**Central Nervous System:** Headaches or dizziness.

**Hemic and Lymphatic Systems:** Transient thrombocytopenia, leukopenia, and eosinophilia. Prolongation in prothrombin time was seen rarely.

**Other:** Genital pruritus, vaginitis, candidiasis.

The following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics.

**Adverse Reactions:** Allergic reactions including anaphylaxis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction, including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE**). If seizures associated with drug therapy occur, discontinue drug. Administer anticonvulsant therapy if clinically indicated.

**Abnormal Laboratory Tests:** Positive direct Coombs test, elevated bilirubin, elevated LDH, pancytopenia, neutropenia, agranulocytosis.

**OVERDOSAGE**

Gastric lavage may be indicated, otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of SUPRAX did not differ from the profile seen in patients treated at the recommended doses.

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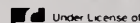
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# Left Ventricular Assistance with the Centrifugal Pump: Management of the Patient with Stunned Myocardium

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**Abstract:** Prompt left ventricular assistance by the centrifugal pump enables the survival of many patients with postoperative low cardiac output who cannot be weaned from cardiopulmonary bypass with the aid of balloon counterpulsation and inotropic agents. Successful weaning from the centrifugal pump, however, depends on the careful selection of appropriate candidates as well as the strict control of pump flow, oncotic pressure, coagulopathy, blood pressure, and systemic afterload. The installation of a hemoconcentration device into the pump line helps control hemodilution and maintain adequate oncotic pressure. The management of a patient who was totally dependent upon left ventricular assistance is described.

An occasional patient with low cardiac output cannot be weaned from cardiopulmonary bypass and does not respond to inotropic agents, balloon counterpulsation, or other pharmacologic and mechanical means of temporary myocardial support. Intraoperative myocardial infarction, insufficient myocardial protection, inadequate cardiac reserve, prolonged ischemic time, metabolic complications, or technical problems may lead to a "stunned myocardium", which is temporarily unable to function independently.<sup>1</sup> An intra-aortic balloon pump (IABP) usually provides sufficient support<sup>2, 3</sup> unless mean arterial pressure falls below 60 mm Hg,<sup>4</sup> which results in arrhythmias and progressive cardiac failure. When balloon counterpulsation is inadequate to restore cardiac output, death is inevitable without the introduction of a left ventricular, right ventricular, or biventricular assist device. With mechanical ventricular assistance, 29% to 40% of patients with postcardiotomy ventricular failure are successfully weaned and discharged from the hospital.<sup>5, 6</sup> Most of these survivors are able to return to gainful employment, with their New York Heart Association functional class improved from class IV preoperatively to class I or II postoperatively.<sup>7, 8</sup> When ventricular assist devices are employed as a bridge of cardiac transplantation, more than half of patients with end-stage cardiomyopathy are able to undergo transplantation.<sup>9</sup> Many of these patients could not have survived otherwise until a donor heart had become available.<sup>10</sup> Since left ventricular assistance is typically attempted first, and right ventricular support added only if left heart support is inadequate, the latter will not be

discussed in this paper. Indications for biventricular assistance and its management are described elsewhere.<sup>11, 12</sup> This paper will outline our management plan for temporary support of the left ventricle by the centrifugal pump (Bio-Medicus, Inc., Eden Prairie, MN).

## Rationale for Choosing the Centrifugal Pump

Although other left ventricular assist devices have been available since the 1970's, the centrifugal pump offers several advantages and improvements in design<sup>11, 14-17</sup> compared with competing devices. The roller pump devised by DeBakey and associates<sup>4, 13</sup> is usually ineffective in supporting circulation for periods longer than 24 hours. Compared to the roller pump, the centrifugal pump 1) minimizes damage to the blood by tubing deformation, 2) reduces red blood cell destruction, 3) decreases particulate embolization, and 4) reduces the need for systemic, complete heparinization. The centrifugal pump has the capacity to pump large volumes of blood without the mechanical trauma associated with compression of the blood and tubing in a roller pump. The current model has a rapidly spinning impeller that propels the blood by centrifugal force, whereas the roller pump propels blood by rhythmic occlusion of plastic tubing within its head. This tubing deformation characteristic of the roller pump causes blood component damage that does not occur with the use of the centrifugal pump. The only original disadvantage of the centrifugal pump, the lysis of red blood cells by motor-generated heat,<sup>16</sup> has been corrected in recent designs.

Sac pumps enable longer mechanical support than the centrifugal pump.<sup>12</sup> However, these devices are generally more expensive, experimental, not widely available to all hospitals, and more often reserved for bridging to transplantation when a donor is not immediately available.<sup>12</sup>

## Selection of Patients for Left Heart Assistance from the Centrifugal Pump

Because of the tremendous undertaking of financial and human resources required to have patients on the centrifugal pump, its use should be restricted to IABP inadequacy or to bridging for heart transplantation. All efforts should be made first to wean patients from cardiopulmonary bypass using IABP and pharmacological means. After attempts to discontinue cardiopulmonary bypass have failed, making the decision immediately to establish a left heart bypass is critical. Any delay can result in irreversible deterioration of vital organs. Magovern<sup>18</sup> discourages multiple, unsuccessful attempts

at weaning before using the device; length of procrastination was the most important determinant of survival in a study of 21 patients on a centrifugal pump. In another study of 43 patients, more than one-third survived when the device was placed during the initial operative procedure whereas only 2 of the 12 survived who had deteriorated in the intensive care unit before placement of the device.<sup>12</sup>

Patients most likely to benefit from centrifugal pump support are those who are young and who have none of the following contraindications. Relatively strong contraindications include severe diabetes mellitus, end-stage cancer, severe refractory pulmonary heart disease, advanced age, and severe metabolic disorders. The only absolute contraindication to left heart bypass with a centrifugal pump is neurological death. Cardiac dysrhythmia should not be considered a contraindication.

The following case report illustrates typical indications for left heart assistance on the centrifugal pump.

### Case Report

A 27-year-old man with a history of hypercholesterolemia and heavy cigarette smoking sustained an antero-septal wall myocardial infarction in June, 1986. After discharge, he noted sporadic episodes of dyspnea and chest pain on mild exertion, which were usually relieved by sublingual nitroglycerine. Cardiac catheterization and coronary angiography performed the next month revealed severe, diffuse, multivessel coronary artery disease and moderate left ventricular dysfunction. He was referred to us for aortocoronary bypass surgery.

On August 1, 1986, we performed a quadruple coronary artery bypass. We used the left internal mammary artery to bypass the left anterior descending coronary artery and the right internal mammary artery to bypass the first obtuse marginal artery. Saphenous vein grafts were used to bypass the second and third obtuse marginal arteries. Because of the severity of the patient's left ventricular dysfunction, retrograde coronary sinus perfusion<sup>19, 20</sup> was used to optimize myocardial protection.

Although the patient initially tolerated weaning off cardiopulmonary bypass after two attempts, low blood pressure made it necessary to reinstate full bypass with IABP support. He tolerated weaning off bypass with the balloon in place and the administration of protamine. He was maintained continuously on dopamine (10 mg/kg/min) and epinephrine (0.5 mcg/min). However, the patient developed severe hypotension and ventricular arrhythmias, fibrillated, and had to be counter shocked. When four successive attempts to wean the patient from bypass failed despite IABP support, left ventricular support was necessary. Cardiopulmonary bypass was reinstituted. A left atrial to right femoral bypass on the Biomedicus® centrifugal pump was installed. The cannula was inserted through the right superior pulmonary vein into the left atrium at a right angle, exited through a separate tunnel to the right of the xiphisternum, and attached to the pump via an outflow line. The left femoral artery was similarly isolated, and a 6 mm Gore-Tex® graft was sewn end-to-side to the common femoral artery because of its

very small size. A 20-gauge aortic cannula was used for return.

The patient was then weaned from cardiopulmonary bypass supported by the centrifugal pump and IABP, and transferred to the Intensive Care Unit, where he developed a severe coagulopathy. Laboratory evaluation revealed a hemoglobin of 7gm., prothrombin time of 35.5 sec, platelet count of 358,000/cu mm, fibrinogen of 110 mg/dl, and partial thromboplastin time of 79 sec. Bleeding from the mediastinal tubes was continuous. Blood volume restoration was instituted with transfusion of fresh frozen plasma, platelets, and red blood cells. He underwent mediastinal exploration which revealed two small venous bleeders. Once controlled, bleeding declined considerably.

Postoperatively, cardiac output remained markedly depressed and totally dependent upon left ventricular assistance. Renal failure and metabolic acidosis followed. With heart transplantation the only recourse, the patient was transferred to another institution for implantation of a Jarvik-7 artificial heart. The centrifugal pump thus became a bridge to transplantation. Upon admission, pump flow had diminished to less than 1L/min/m<sup>2</sup>, and neurological evaluation revealed advanced ischemic encephalopathy, which did not respond to measures to improve blood flow through the pump. Due to evidence of brain death, support was discontinued, and the patient expired August 3, 1986.

This patient was considered an excellent candidate for left ventricular assistance on the centrifugal pump. Nevertheless, as in many similar cases of severe left ventricular dysfunction, he was unable to recover from left ventricular failure despite heroic efforts. His unexpected neurological death made continued support leading to heart transplantation unfeasible.

### Preparation for Left Ventricular Assistance with the Centrifugal Pump

Preparation of a candidate for centrifugal pump left heart assistance is aggressive, and the technical and paramedical personnel must understand the critical nature of the situation. A strict management plan must be established rapidly and then followed, with exceptions only to react to immediate circumstances. Laboratory tests must be planned, and nursing personnel must be informed that this is not routine postoperative open heart surgery patient.

### Laboratory Tests

A schedule of laboratory assessments must be established. We follow this schedule for basic monitoring:

- 1) Arterial blood gases and serum potassium every hour;
- 2) Hemoglobin and hematocrit, platelets, prothrombin time, partial thromboplastin time, fibrinogen, fibrin degradation products, and ionized serum calcium every two hours;
- 3) Electrolyte panel every four hours;
- 4) Blood urea nitrogen (BUN) and serum creatinine every 12 hours;
- 5) SMA-18 every 24 hours.



## Cannulation

To provide adequate flow on the centrifugal pump, cannulas of adequate size must be placed. The left ventricle can be accessed via the left atrial appendage,<sup>13, 15, 21-25</sup> the right superior pulmonary vein,<sup>11</sup> or the apex of the heart.<sup>15, 22, 25-28</sup>

Cannulation through the left atrial appendage is an appealing choice because it is readily accessible. However, the left atrial appendage is friable and easily torn. Besides, the sutures used for cannulation can necrose the appendage over the course of days because of their "purse string" effect. As a result, the cannulation site becomes even more friable and may bleed excessively. Furthermore, the closure of a necrotic atrial appendage is difficult later when the bypass is being disconnected. All of these problems, compounded by the possibility of tissue impingement into the atrial cannula leading to diminished flow, have practically eliminated the use of this approach.

We recommend cannulation of the left atrium via the right superior pulmonary vein. Access is relatively easy, and the tissue of the pulmonary vein is not as friable as that of the left atrial appendage. Furthermore, occlusion by tissue of the left atrial cannula is unlikely and, if desired, the cannula can be directed easily through the mitral apparatus. The primary disadvantage of pulmonary vein cannulation occurs during removal, when the heart must be compressed to decannulate the atrium and repair the pulmonary vein. Initially, the surgeon may attempt decannulation and pulmonary vein repair without resorting to cardiopulmonary bypass. If needed, temporary normothermic cardiopulmonary bypass can be implemented to repair the pulmonary vein in those patients who do not tolerate cardiac compression.

Cannulation of the left ventricle through the apex of the heart provides fast access to enable the rapid initiation of left heart bypass. The main disadvantages of this approach are that 1) once the apex is cannulated, repair of the apex is difficult, and 2) the apex becomes practically immobile. We suggest using the apex for cannulation only if the decision has already been made to proceed directly to cardiac transplantation.

## HEMODYNAMIC MANAGEMENT

### Blood Product Replacement

Coagulopathy is inevitable in candidates for left ventricular assistance because of the lengthy procedure and cardiopulmonary support while attempts were made to wean the patient from bypass. Therefore, blood component replacement must begin within the first hour of centrifugal pump support. Our plan obviates the need for heparin anticoagulation by mandating maintenance of pump flow greater than 1 L/min. Slower flow rates are associated with thrombotic phenomena and consequently, either the flow must be increased or full heparinization implemented.

Red blood cells are replaced as needed and fresh frozen plasma administered at the rate of one unit per hour. Fresh frozen plasma and human serum albumin (5%) become the replacement fluids for these patients.

Frequent coagulograms should guide the administration of platelets and cryoprecipitate plasma.

### Management of Colloid Oncotic Pressure

Often, all blood flow in the centrifugal pump left heart assist is either nonpulsatile or pulsed only by the effect of an IABP. Nonpulsatile flow in the intact human tends to cause fluid shifts into the interstitium ("third-spacing"). Colloid administration in the form of concentrated albumin compensates for third-spacing by increasing colloid oncotic pressure and thereby drawing water back into the vascular tree. Pump flows and filling pressures guide volume administration. High filling pressures are necessary to achieve physiologic pump flows. A minimum of 2.0 L/min/m<sup>2</sup> should be the goal for pump flows. The recommended minimum fluid replacement regimen is the hour-by-hour replacement of the urine output with 25% albumin for the first 100 cc and 5% albumin for the remaining volume. Crystalloids are not recommended for volume replacement because of their tendency to migrate to the interstitium.

Since 1986, we have included a hemoconcentration device in the centrifugal pump line. Hemoconcentration by blood ultrafiltration has been recommended to control hemodilution and help reduce blood loss while preserving plasma proteins during open heart operations.<sup>28</sup> This method has yielded similar results in our patients supported by centrifugal pump left ventricular assistance. By using ultrafiltration in conjunction with albumin administration, we have achieved a satisfactory oncotic pressure while preserving adequate renal function. With this regimen, we have observed a rather dramatic reduction in tissue edema in patients on the centrifugal pump.

### Mediastinal Re-exploration

Constant or rapid blood loss through the mediastinal tubes is an indication for mediastinal exploration with the goal of reducing blood component administration. For this reason, we do not close the sternum of the patient on left heart bypass. Instead, we cover the heart with sponges soaked in Betadine® and apply an occlusive plastic drape over the chest wall. The problem of blood entrapping the heart in the mediastinum far outweighs the risk of re-exploration. By leaving the sternum open and the entire area covered with a plastic drape, rapid re-exploration can be performed with minimal mobility and preparation.

## PHARMACOLOGIC MANAGEMENT

### Anticoagulation

The centrifugal pump requires less anticoagulation than the roller pump. Low-dose heparin, sufficient to prolong the clotting time by 50%, can be used to maintain flow between 1 and 3 L/min. We believe, however, that if the flow is greater than 1 L/min, anticoagulation with heparin is really unnecessary. In the absence of anticoagulation, low molecular weight dextran (10% dextran-40 in normal saline), at the rate of 20 cc/hour is administered to improve blood rheology.

Frequent assessment of the coagulogram, prothrombin time, partial thromboplastin time, fibrin split products, fibrinogen, and thrombin time should be performed and abnormalities corrected. Because the pump heads accumulate particulate matter, they should be replaced every 48 hours.

### Blood Pressure Support

Maintaining an adequate blood pressure to perfuse vital organs may require the use of multiple drugs. First-line drugs include dopamine,<sup>29-32</sup> norepinephrine,<sup>29, 31</sup> neosynephrine, calcium chloride, and sodium bicarbonate.

Dopamine is the first choice because of its wide spectrum of actions. In low doses (0.5 to 5 mcg/kg/min), dopamine improves flow to the kidneys and mesenteric organs.<sup>32</sup> In moderate doses (5 mcg/kg/min), it produces a positive inotropic effect. In high doses (greater than 10 mcg/kg/min), it has an almost pure alpha vasoconstrictive action, and effect identical to that of norepinephrine.

Norepinephrine is used only when dopamine fails. It may also be used in conjunction with other agents to reduce the amount of individual drugs required or to promote synergism between several agents. Doses of .03 to .5 mcg/min can be used for patients on left ventricular assistance. Because of its side effects, weaning from norepinephrine is highly desirable.

When other primary agents have failed, neosynephrine may be used to raise arterial blood pressure by rapidly increasing peripheral vascular resistance. This potent agent is likely to have a rapid and profound effect. Rebound hypotension during neosynephrine withdrawal has been reported.<sup>33, 34</sup>

Calcium chloride must be replaced when blood transfusions are given. One gram of calcium chloride should be administered for every 5 to 6 units of packed red blood cells.

Sodium bicarbonate is used frequently to rapidly correct metabolic acidosis, since all cardioactive and vasoactive catecholamines function in a relatively narrow pH range. Because overzealous administration of sodium bicarbonate carries its own hazards, administration must be guided by frequent arterial blood gas analyses.

Adrenaline, a second-line drug used to increase blood pressure, may prove very useful if vasodilation is severe. Doses in the range of 0.09-0.05 mcg/min may be necessary to promote vasoconstriction.

Dobutamine should not be used initially because of its combined inotropic and vasodilator properties. This drug can exhibit profound inotropic action on cardiac muscle with a small increase in myocardial oxygen demand.<sup>30, 31</sup> Dobutamine is usually reserved for times when myocardial activity has improved, such as when weaning from bypass.

### Afterload Management

Management of systemic afterload is critical to the success of a left heart bypass with the centrifugal pump. The centrifugal pump is an afterload-sensitive pump. Therefore, its ability to pump large volumes of blood efficiently is severely impaired by increases in afterload

(high peripheral vascular resistance or excessive systemic pressure).

A fine balance must be achieved in the management of hemodynamics. Systemic blood pressure per se is less important when the patient is on left heart bypass. Maintenance of a mean blood pressure of 60-70 mm Hg is adequate for tissue perfusion in most cases. Throughout all the phases of left heart bypass, systemic afterload control is mandatory. Virtually all patients benefit from a low-dose infusion of nitroprusside for afterload management. Although a systemic vascular resistance (SVR) of 600-700 dynes/sec/cm<sup>5</sup> is ideal, an SVR of 400-500 is acceptable. However, a normal SVR of 800-1200 is too high for a patient requiring left heart bypass. High systemic vascular resistance interferes with the performance of the centrifugal pump.

### Nutritional Support

Beginning total parenteral nutrition (TPN) immediately after the initiation of left ventricular assistance is mandatory. The extreme stress, high metabolic demands, and general poor condition of these patients can result rapidly in a negative nitrogen balance. Therefore, the volume of TPN must be balanced carefully with the total volume of fluids given to the patient, and BUN, serum creatinine, osmolality, and electrolytes must be monitored frequently.

### Antimicrobial Agents

All patients on the centrifugal pump are given a third generation cephalosporin intravenously. Cultures are taken from the mediastinum, urine, and blood if the patient develops fever or the white blood cell count rises. Antimicrobials are selected according to their sensitivity to any specific organism isolated.

### Weaning Techniques

The patient's status should be assessed frequently to determine the feasibility of weaning from left heart bypass. We recommend a cautious approach. After a period of total support, centrifugal pump support is reduced by approximately 20 to 25%. To provide a baseline for comparison, cardiac output is assessed by thermodilution after an equilibration period of 15 to 20 minutes. If other measures such as arterial pressure, pulmonary artery pressure, central venous pressure, and heart rate remain stable, cardiac output is reassessed 45 to 60 minutes after the pump flow has been reduced. If the contribution by the heart is sufficient, the thermodilution cardiac output should remain relatively stable as the pump flow is decreased. If the second cardiac output reflects a significant contribution by the heart to the total cardiac output, weaning may proceed. If the heart does not contribute significantly, the weaning attempt should be terminated and the patient returned to full flow for another 4 to 6 hours before another attempt is made. Pharmacologic assistance, as well as intra-aortic counterpulsation, should be employed to bolster cardiac output as needed.

Weaning should be undertaken gradually over the course of 2 to 4 hours. Once it has been determined that the patient can be weaned, there should be no delay in



promptly terminating left ventricular assistance. The technique of removing the device is determined by the method and site of cannulation. In any case, the centrifugal pump must be discontinued in the operating room by a full staff. During weaning, adequacy of anticoagulation should be assessed frequently and controlled. At this point, full systemic heparinization, that is, greater than 3 mg/kg, should be administered if the pump suction or the cardiopulmonary bypass machine must be employed. The mediastinum is exposed, blood evacuated, and clots removed. The pump lines are isolated and the tourniquets and safety lines identified. The pump is stopped, and the atrial line to the pump is clamped to prevent shunting back to the atrium. Pump suction is used to salvage shed blood, which is returned to the patient through the aortic cannula. The atrial cannulation site is freed and the tourniquets loosened. The cannula is removed and the tourniquets tightened and tied. The cannulation site is oversewn.

### Management of the Patient After Left Heart Assistance

Management of the patient after weaning from left heart bypass on the centrifugal pump is similar to that of any patient who has an IABP in the acute phase after an open heart procedure. The following exceptions and precautions must be noted, however.

After left heart bypass, the patient is still very afterload-sensitive. Systemic vascular resistance must be maintained strictly within the 600-900 dynes/sec/cm<sup>5</sup> range. Nitroprusside is the drug of choice unless documented thiocyanate toxicity calls for the use of a substitute. Notably less potent, nitroglyceride acts markedly on capacitance vessels and tends to promote pulmonary shunting. At this point, the introduction of amrinone (Inocor®) may prove to be crucial. This very potent agent is known to decrease afterload while having a very profound inotropic effect. Although multiple drug use may be optimal, care must be taken to avoid introducing agents that may counteract the effects of other agents. Total parenteral hyperalimentation should be continued to maintain appropriate nutritional support.

Weaning from the IABP should not be attempted until 6 to 10 days after weaning from the centrifugal pump. The insult that necessitated the use of left ventricular assistance is not resolved simply because weaning was successful. The IABP may assume an important role in allowing myocardial recovery.

Weaning from the ventilator also should be very cautious. The ability to control the patient's blood gases, pH, and other measures with the ventilator is highly desirable.

The prevention and management of dangerous arrhythmias is crucial. Arrhythmias can be expected to follow weaning and distention of the heart. Prophylaxis with lidocaine may be a necessary adjunct to weaning.

Continued antimicrobial prophylaxis is also essential. To discourage infection, indwelling lines and catheters should be changed frequently.

### Conclusion

Temporary mechanical left heart assistance enables the survival of 15-37%<sup>13, 15, 17, 18, 23, 36</sup> of patients with low

cardiac output who cannot be weaned from cardiopulmonary bypass after open heart surgery. However, most of the various devices employed to provide long-term support of the failing heart require continuous, systemic heparinization of the patient and produce damage to blood components. Long-term anticoagulation with left ventricular assistance frequently results in fatal complications. By maintaining a minimum blood flow of 1 L/min and changing the pump at least every 48 hours, we are able to provide long-term myocardial support on the centrifugal pump with negligible thromboembolism even when little or no anticoagulation. Blood loss, damage to blood components, and hemodilution are reduced by installing a hemoconcentration device in the pump line. Further improvements in reducing the risk of thromboembolic complications await the investigation of thromboresistant surfaces.<sup>37</sup> Newer methods of left heart bypass,<sup>38</sup> such as the promising left ventricular assist system under development by Norman<sup>39</sup> and Frazier,<sup>40</sup> are also under clinical investigation. In the future, patients who cannot be weaned from cardiopulmonary bypass or who are awaiting a donor heart may be supported routinely by the Nimbus HEMOPUMP\*, a small ventricular assist device now in use by Frazier and colleagues.<sup>41</sup>

**Resumen:** Existe un grupo de enfermos que no pueden separarse del aparato cardiopulmonar después de cirugía a cielo abierto aunque se utilice el balón intra-aórtico y/o agentes inotrópicos. Muchos de estos pacientes pueden recuperarse y prolongar su vida si se utiliza un mecanismo de asistencia al corazón izquierdo (Left Heart Assist Device-IVAD).

Nuestro grupo utiliza la bomba centrífuga como mecanismo de asistencia. Para evitar que el paciente se deteriore se debe utilizar mecanismo de asistencia tan pronto se determine que el paciente no puede sostener su gasto cardíaco con el balón intra-aórtico solamente.

Recomendamos la canulación del atrio izquierdo através de la vena pulmonar derecha superior. La aorta ascendente se canula como se hace rutinariamente y el flujo de la bomba se mantiene sobre un litro por minuto para evitar embolias, ya que preferimos no usar heparina. Concentrados de albumina se administran para compensar con los cambios en flujo de fluidos que ocurren en el intersticio del paciente (tercer espacio). Para mantener una presión oncótica satisfactoria instalamos un hemoconcentrador al circuito.

Como las cuagulopatías se observan frecuentemente, el esternón se deja abierto y esto nos permite la rápida exploración del mediastino si el paciente pierde una cantidad excesiva de sangre. En el manejo de estos pacientes hay que usar farmacos para mantener la resistencia periférica baja y un nivel de presión sistémica adecuado para perfundir los órganos del cuerpo.

La separación de los enfermos de el mecanismo de asistencia usualmente es un proceso gradual que toma entre dos y cuatro horas. Este artículo describe el manejo clínico de un enfermo completamente dependiente en la bomba centrífuga de asistencia del ventrículo izquierdo (LVAD).

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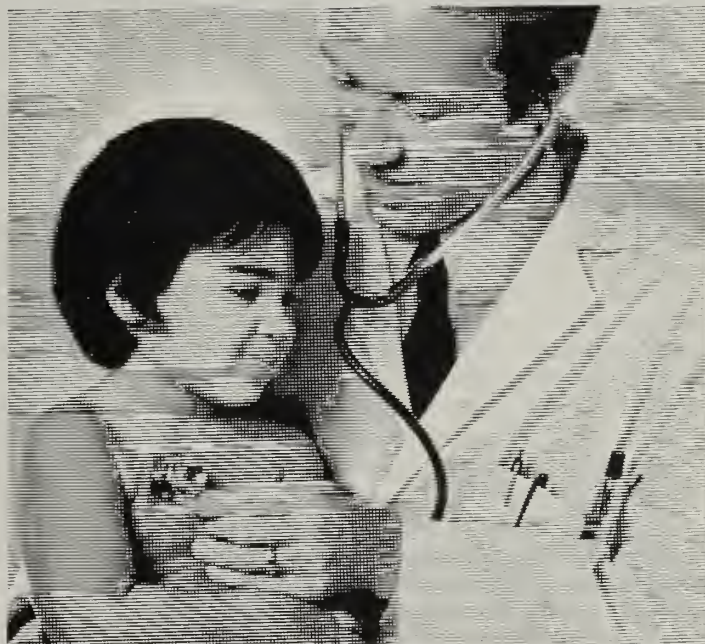
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## CONTINUED MEDICAL EDUCATION

### Initial Evaluation of the Asthmatic Patient

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**Summary:** Bronchial asthma is a common disease that is not yet completely understood. We specify the basic evaluation that asthmatic patients should undergo and discuss some aspects of pathophysiology. Guidelines to select patients for further evaluation are suggested.

The contemporary relevance of asthma derives from its substantial prevalence (around 3% in the USA) and a mortality which is small (3 deaths per 1,000,000 people per yr.), but may be increasing.<sup>4</sup> It has complex mechanisms. A single exposure to a precipitant may produce not only initial bronchospasm (the early asthmatic response), but may be followed hours later by renewed bronchospasm and an inespecific bronchial hyper-reactivity (the late asthmatic response) that may last hours or days.

Asthma is also a multifactorial condition. It would be hard to say that an atopic boy, a middle aged woman with symptoms after work and an elderly smoker have the same disease. Despite multiple investigations, we have been unable to come up with a better definition than the one adopted by the American Thoracic Society in 1962: "the presence of widespread narrowing of the airways which alters in severity either spontaneously or in response to treatment and which is characterized by increased responsiveness of the trachea and bronchi to various stimuli".<sup>1</sup> Thus, we may think of asthma as a final common pathway to a variety of pathophysiological events with bronchial hyperreactivity as their common denominator. Fortunately, it is a generally benign condition for which excellent medical therapy is available and whose initial evaluation does not have to be complicated. Here we discuss the initial evaluation of the asthmatic patient underscoring the physiologic basis of the observed symptoms and signs.

#### History

The most common symptoms of asthma are episodic wheezing, dyspnea, cough and chest tightness. Unfortunately, these symptoms are not specific for asthma and may not be present in all patients. Even wheezing, still regarded by some practitioners to be the *sine qua non*, of

asthma, may be absent.

Historical evaluation should include detailed questioning for known precipitating factors (table 1). Job related symptoms should be sought (table 2). The time between potential exposures and symptoms should be identified since early, late, or both types of reactions, may be present. Viral infections can precipitate attacks on asthmatics or produce transient bronchial hyperreactivity for up to eight weeks in a non asthmatic. Thus, the occurrence of a recent viral upper respiratory tract infection should be investigated. The presence of respiratory symptoms in relatives should also be determined.

Table 1

#### Common Precipitants of Asthma Attacks

Physical stimuli - Exercise, hyperventilation, breathing cold air  
Foods - Milk, nuts, eggs, coloring agents  
Preservatives - Metabisulfites, monosodium glutamate  
Medications - Aspirin, beta blockers (including eyedrops)  
Allergens - Pollens, animal danders, house dust components, molds  
Air pollution  
Viral infection of the airways

Table 2

#### Bronchial Sensitizers in the Work Environment

Laboratory animal products - Laboratory workers, veterinarians, animal handlers  
Bird products - Pigeon breeders, poultry workers, bird fanciers  
Insect products - Entomologists, field workers, grain workers, researchers  
Plant products - Grain handlers, bakers, millers, food, tobacco and oil industry workers, brewery chemists, printers, carpentry, sawmill and construction workers  
Diisocyanates - Polyurethane, plastic and varnish industries, foundry workers, auto spray painting  
Anhydrides - Epoxy, resin and plastic industry workers  
Metals - Hard metal and refining industry workers, metal plating, tanning  
Drugs - Pharmaceutical and chemical industry workers, brewers, livestock breeders  
Fluxes - Solderers  
Other - Crab and prawn processing, hairdressing, photography, dye and photocopying, hospital staff, refrigeration and insulation



### Physical Examination

Tachypnea, wheezing, prolongation of the expiratory phase, reduced breath sounds and hyperresonance may be present in the asthmatic patient. However, the physical examination may be unrewarding between attacks. In severe bouts use of accessory respiratory muscles may be apparent, the anteroposterior diameter may increase, and the presence of a drop of more than 10mm of mercury of the systolic blood pressure during inspiration —pulsus paradoxus— may be observed.

The nasal cavity should be examined for pale or boggy mucosa, nasal polyps or discharge. Control of inflammatory disease of the upper airways impacts positively on the manifestations of asthma. Careful recording of the symptoms and physical findings is the most useful tool to follow patients and identify the presence of an exacerbation.

### Pathophysiology

Severely impaired airflow through constricted, edematous, mucus-filled airways may cause a decrease in breath sounds. The cross sectional area of bronchi is further reduced during expiration. Thus the expiratory phase is prolonged. Turbulent flow through the constricted airways causes wheezing.

Since airways collapse during exhalation, there will be air trapping producing hyperresonance. When the resting position of the chest wall changes from normal to hyperinflated, the respiratory muscles are placed at a mechanical disadvantage. The unevenness of the process results in ventilation perfusion mismatch and mild hypoxemia. The hypoxemia, increased airway resistance and muscular mechanical inefficiency causes dyspnea with tachypnea and use of accessory muscles. The hypocarbia often observed is a consequence of the increased alveolar ventilation needed to maintain adequate blood oxygenation.

Pulsus paradoxus is the result of shifting of the inter-ventricular septum towards the left ventricle during inspiration. This is caused by decreased inspiratory intrathoracic pressures with increased venous return. This shift produces reduced left ventricular end-diastolic volumes with subsequent reduction in stroke volume and a drop in systolic blood pressure.

### Laboratory Evaluation

The initial evaluation of the asthmatic patient should include a complete blood cell count, postero-anterior chest film, spirometry and sputum examination.

The cell count will usually be normal. An elevated white cell count may suggest the presence of infection. An eosinophil percentage of five or more may indicate atopy. Persistent hypoxemia will produce an increase in hemoglobin concentration but this is not expected in the asthmatic patient.

The chest film is also usually normal. Hyperinflation and peribronchial cuffings can occur during decompensations. In the absence of unexpected symptoms or signs, it is unnecessary to repeat chest films for asthmatic exacerbations.

Spirometry is indispensable to quantify airway obstructions, show the extent of the response to bronchodi-

lators. A normal spirometry is expected between attacks and does not rule out the diagnosis. In such cases, bronchial challenge with methacholine, non-isotonic saline or cold air may be needed to document the presence of bronchial hyperreactivity.

Examination of purulent looking sputum is important. A predominance of neutrophils suggests bacterial infection. When eosinophils predominate, antibiotic therapy is not indicated. The sputum may also show bronchiolar casts (Curschmann's spirals), clumps of epithelial cells with moving cilia, and elongated octahedral spicules (Charcot-Leyden crystals). Brown plugs or bronchial casts raise the possibility of allergic bronchopulmonary aspergillosis and should prompt a preparation of the sputum with 10 per cent KOH for microscopic exam and culture for fungi.

During an acute attack of asthma it is of the utmost importance to determine how severe is the obstructive impairment. This is best done by a combination of physical examination and spirometry. The degree of tachycardia, tachypnea, use of accessory muscles and the presence of absence of pulsus paradoxus and/or cyanosis all help the clinician gauge the patients condition. Spirometry is probably more reliable than any of the physical signs. In cases of moderate to severe ventilatory impairment, arterial blood gases may help decide when intubation is appropriate.

### Comments

Uncomplicated asthma can be treated by physicians with varied training backgrounds. When the diagnosis is not clear, or patients do not respond readily to therapy, consultation with a pulmonary specialist is in order. Findings in the history, physical examination or laboratory evaluation other than those previously described as typical of asthma should alert the physician that other diseases may be present. Patients that do not respond to therapy or that show poor response as evidenced by the persistent need for systemic steroids or frequent hospitalizations or visits to the emergency room, should also be consulted. Three hospitalizations or emergency room visits in 6 months show poor asthma control and are considered by some as evidence of incapacitating disease.

Asthma should be differentiated from cardiac failure, airway obstruction by tumor or foreign body, bronchitis, emphysema, pulmonary embolism, cystic fibrosis, bronchopulmonary aspergillosis, bronchiolitis obliterans and other more uncommon diseases. The pulmonary specialist, depending on the initial evaluation may request tests for lung volumes, diffusing capacity, arterial blood gases, spirometry before and after bronchodilators, bronchial challenge testing, radiologic imaging studies, ventricular function studies, skin testing for common aeroallergens or total serum IgE, which seems to correlate better with asthma than common aeroallergen skin testing.<sup>5</sup>

**Resumen:** El asma bronquial es una condición común que aún no entendemos completamente. Aquí presentamos la evaluación básica que debe hacerse a todo paciente asmático y discutimos algunos aspectos patofisiológicos. También sugerimos guías para seleccionar aquellos pacientes que deben ser evaluados más profundamente.

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## CME QUIZ

1. The mortality of asthma is
  - a) high
  - b) low and seemingly decreasing
  - c) low but seemingly increasing
  - d) zero
2. The symptoms of asthma
  - a) always include wheezing
  - b) may consist only of dyspnea of chest tightness
  - c) always include cough
  - d) both a and c
3. Asthma attack precipitants include
  - a) allergens and air pollution
  - b) foods and preservatives
  - c) physical stimuli and medications
  - d) all of the above
4. The signs of asthma
  - a) may include tachypnea and wheezing
  - b) occur only on the expiratory phase
  - c) always includes pulsus paradoxus
  - d) are secondary to hypoxemia
5. The basic evaluation of the asthmatic patient includes
  - a) spirometry and complete blood-cell count
  - b) P-A chest film and skin testing for common aeroallergens
  - c) sputum examination and diffusing capacity
  - d) all of the above
6. The P-A chest film of the asthmatic patient
  - a) should be repeated for each exacerbation
  - b) is seldom, if ever, normal
  - c) may show hyperinflation and/or peribronchial cuffing
  - d) usually shows a pulmonary infiltrate
7. Spirometry
  - a) is not necessary to gauge the severity of airways obstruction
  - b) can be used to measure the effect of bronchial challenge tests
  - c) is always abnormal
  - d) is of no use to quantify response to bronchodilators
8. The severity of an asthmatic attack is best gaged by
  - a) Physical examination
  - b) spirometry
  - c) both
  - d) neither
9. Patients that should be consulted to a pulmonary specialist
  - a) Patients who need prolonged therapy with systemic corticosteroids
  - b) patients with an unclear diagnosis
  - c) patients requiring frequent hospitalizations
  - d) all of the above
10. The differential diagnosis of asthma includes
  - a) airway obstruction by tumor or foreign body
  - b) bronchitis and emphysema
  - c) cystic fibrosis and bronchiolitis obliterans
  - d) all of the above





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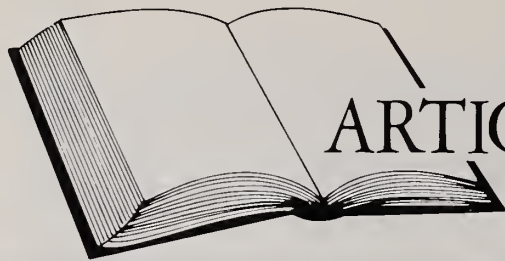
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# ARTICULOS DE REPASO

## Cólico Infantil

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Carmen E. Lugo, MD

**Resumen:** Al revisar la literatura, encontramos que hay varias teorías implicadas en el síndrome de "cólico infantil". Tanto las causas gastrointestinales como las de interacción, comportamiento y temperamento han sido consideradas.

Se han revisado recomendaciones para el manejo y tratamiento basado en ambas teorías. Estas han probado ser útiles y exitosas en muchos casos. Finalmente, reconocemos la necesidad de más investigación en el futuro en torno a esta condición.

Como médicos primarios, muchas veces nos encontramos con condiciones que causan mucha tensión familiar y que pueden ser motivo, en ocasiones, de controversia entre los familiares. La condición que discutimos es una de ellas; cólico infantil. A continuación un repaso de la literatura médica.

### Introducción

El llanto en la infancia tiene varios propósitos fisiológicos: marca el comienzo de la respiración al nacer, es una vocalización refleja que representa un intento de comunicación del infante, y puede ser el primer paso hacia el desarrollo del lenguaje.<sup>1, 2</sup> Además, tiene propósitos neurofisiológicos importantes ya que el infante ante un estímulo puede acumular tensión que luego podría ser liberada a través del llanto y así mantener su homeostasis interna.<sup>3</sup> El llanto en sí tiene cierta regularidad y no puede ser eliminado por completo. Encontramos que bebés sanos y saludables lloran con cierta regularidad, y por lo tanto, podemos asumir que hasta cierto nivel, éste es normal en nuestra cultura. Luego de nacer, la calidad del llanto comienza a diferenciarse y es distinto dependiendo de las necesidades fisiológicas del infante; (ej), hambre, cambios en temperatura, dolor e incomodidad.<sup>2</sup> El infante espera una respuesta de su madre o de la persona que lo cuida para

que le alivie o calme su condición. Si la tensión alrededor del infante empeora, y el problema no es resuelto, éste llanto se agrava, se prolonga y puede ser el precursor del cólico infantil. Para algunos padres, sobre todo los inexpertos, el no poder resolver esta situación puede representar el que ellos no sean "buenos padres" y se encuentren inefectivos en el manejo rutinario de un infante. Al tratar de compensar por esta "falla", se aumenta la tensión alrededor del infante y esto puede agravar la situación.

### Definición de cólico

Podemos definir cólico como un llanto excesivo de causa desconocida en infantes completamente sanos. El tiempo promedio que dura esta condición es aproximadamente los primeros tres meses de vida. Además, debemos incluir que en la mayor parte de las ocasiones, la queja de los padres excede la proporción del problema. Esto se puede deber a una serie de factores. Los padres creen, en su mayoría, que ya para el mes de vida el bebé debe dormir toda la noche. Para algunas personas el dormir toda la noche implica dormir de 8-10 horas, mientras que para otras puede ser menos horas. Moore<sup>4, 5</sup> revela en su estudio que el 70% de los infantes duermen la noche completa ya para los tres (3) meses de edad; el 83% de los infantes lo hacen para los 6 meses de edad y el 90% lo logra para los nueve meses de edad. Sin embargo, en otros estudios, los infantes de 9 meses se despertaban en algún momento durante la noche en alrededor de un 22-29%. Los períodos de sueño aumentaron progresivamente de 4-5 horas al nacer y de 8 a 10 horas para los 3-4 meses en su gran mayoría.<sup>6-7</sup>

Frecuentemente, los padres no pueden controlar la situación con ningún método rutinario. El llanto debe ser uno fuerte y consecutivo, que dure en muchas ocasiones más de tres horas al día y que pueda ocurrir repetidamente en un promedio de tres a cuatro días a la semana.

Todos estos bebés se encuentran sanos, se alimentan adecuadamente y están contentos entre estos ataques de llanto.

El cólico comienza usualmente en el primer mes de vida, con más frecuencia durante la primera semana. El



llanto ocurre intermitentemente durante el día y la noche y dura usualmente entre 30 minutos y 3 horas. Esto está basado en el estudio de Brazelton que encontró que a las 2 semanas de vida los bebés lloraban un promedio de 1.75 horas/día; a las 6 semanas, un promedio de 2.75 horas/día y a las 12 semanas un promedio de 1.0 horas/día.<sup>3</sup>

Estos bebés presentan, además, unas características físicas tales como endurecimiento del abdomen, flexión de las extremidades inferiores, gases, flatulencia, y rubor en el momento del ataque. Esto hace pensar a los padres en la posibilidad de que el bebé tiene dolor abdominal y/o problemas gastrointestinales. Esta condición es común y puede ocurrir en 10-15% de los infantes,<sup>8</sup> pero varía de un 10 a un 30%.<sup>9, 10</sup> La incidencia en bebés prematuros es la misma, pero se ha encontrado que se pospone su comienzo hasta que el infante prematuro tiene una edad gestacional de 39 a 44 semanas, lo que podría sustentar una base fisiológica.<sup>8</sup>

El cólico no tiene predilección por sexo; ocurre tanto en los varones como en las hembras. En la mayor parte de los casos hay una tendencia familiar y en casos severos de cólicos el 50% de los hermanos han tenido ésta misma condición.<sup>8</sup>

### Evaluación

Al presentar un paciente con llanto (cólico) debemos iniciar nuestra búsqueda hacia la causa que lo provoca. Debemos tomar un historial completo y un examen físico exhaustivo e identificar si éste es un problema agudo o crónico. Si esto es un primer episodio, debemos saber si hay una causa orgánica o si es una variante normal. Si se determina que es un problema recurrente debemos distinguir también si se debe a alguna causa orgánica o si nos encontramos con un paciente con cólico infantil.<sup>11</sup>

Las causas orgánicas que provocan comúnmente sintomatología de llanto son las siguientes: otitis media, congestión nasal, estreñimiento, uso de medicamentos tales como descongestionantes o antihistamínicos que tienen efectos secundarios, síndrome de retirada de drogas, tales como heroína o metadona e infecciones urinarias. A tales efectos, inicialmente, un buen historial y examen físico nos ayudarán a establecer un diagnóstico, pero debemos ordenar un análisis de orina para descartar infección urinaria. Du<sup>12</sup> reportó cuatro casos de infantes cuyo único síntoma de infección urinaria fue cólico recurrente y persistente. Otros diagnósticos pueden ocasionar dolor, malestar y llanto en un infante. (Ver Tabla I) El efecto de fumar en familiares, ha sido reportado por Said<sup>13</sup> como causa no orgánica de cólico e irritabilidad en el infante. La incidencia de cólico era mayor en aquellas familias en donde el consumo de cigarrillos era elevado.

### Causas Gastrointestinales

Es de todos conocido que en pacientes que presentan malabsorción, los carbohidratos no se absorben adecuadamente en el segmento proximal del intestino delgado. Estos llegan al colon en donde se fermentan por las bacterias allí presentes formando ácidos orgánicos de cadena corta e hidrogeniones. Estos ácidos orgánicos se absorben por la mucosa colónica o se excretan en las

Tabla I

Causas Orgánicas de Llanto Persistente	
General:	Síndrome de alcohol fetal, falla en crecimiento pondostatural
2- Ojos, Oídos Nariz y Garganta:	Abrasión de la córnea; cuerpo extraño en el ojo (pestaña); glaucoma; congestión nasal; faringitis; moniliasis oral; gingivostomatitis; otitis media
3- Cabeza y Cuello:	Meningitis; fractura de cráneo; hematoma subdural; enfermedad de Caffey
4- Gastrointestinales:	Estreñimiento; gastroenteritis; fisura anal; hernia inguinal; intususcepción; reflujo gastroesofágico, vólvulo; apendicitis; intolerancia a la proteína de la leche; intolerancia a lactosa
5- Cardiovasculares:	Fallo congestivo; taquicardia supraventricular
6- Genitourinarias:	Infección de orina; obstrucción de tracto genitourinario; torsión de testículo; moniliasis genital
7- Esqueletales:	Fracturas; osteomielitis; artritis; pedazo de hilo o cabello que se enrolla alrededor de un dedo, síndrome del niño maltratado
8- Piel:	Exantema prurítico o doloroso (ej. área del pañal), quemaduras

heces en forma de sales de sodio o de potasio. El 15% del gas que se produce se absorbe al torrente sanguíneo y el resto sale como flatulencia. Una teoría que se ha querido implicar en cólico, es que el dolor pueda ser secundario a aumento de gases intestinales. Algunos han descrito que estos pacientes tragan mayor cantidad de aire y otros que estos pacientes presentan dificultad en deshacerse de los gases. El dolor es causado por el aumento súbito de distensión de la víscera. Sin embargo, se ha encontrado que estos pacientes con cólico, en su mayoría, no tienen un aumento excesivo de gas intestinal por radiografías.<sup>10</sup> Liebman<sup>14</sup> y Stahlberg<sup>15</sup> no encontraron ninguna relación entre malabsorción de lactosa y cólico. También se ha implicado alergia a la leche de vaca como posible etiología en el cólico infantil.<sup>9, 16</sup> Estos estudios enfocan los componentes proteicos como los causantes del problema, aunque la colitis inducida por la proteína de la leche se encuentra en un 0.5-2.0% de los niños.<sup>8</sup>

Jakobsson<sup>16</sup> reportó que un 50% de los infantes con cólico que recibían leche materna no se aliviaban cuando a la madre se le quitaba la leche de vaca de su dieta. Lothe<sup>9</sup> demostró que 32 de 60 infantes (53%) que recibían leche de vaca y/o leche de soya no mejoraron cuando se cambiaron a un hidrolizado de proteína.

Por el contrario, Liebman<sup>14</sup> concluyó en su estudio que la alergia a la proteína de la leche no era significativa como causa de cólico ya que no hubo un aumento en IgE en 56 infantes con cólico cuando se les suministró leche de vaca. Thomas<sup>17</sup> concluyó también que hipersensibilidad a la proteína no era la causa de cólico en pacientes sanos. Intolerancia a la proteína de la leche se podría considerar como causa de cólico en aquellos pacientes en donde se demuestre evidencia de daño intestinal o síntomas sistémicos como urticaria, sibilancias, rinitis crónica y otitis media. Estos pacientes presentaban un historial positivo de alergia en la familia.

Otros componentes que se han considerado en la etiología de cólico es el contenido de hierro en la fórmula. Algunos médicos evidencian mejoría en síntomas tales como irritabilidad, diarrea, cólico, estreñimiento, y

vómitos cuando usan una fórmula libre de hierro. Oski<sup>18</sup> en su estudio no encontró ninguna diferencia entre pacientes a los cuales se les ofreció leche fortificada con hierro y leche sin hierro. No hubo ningún aumento en los síntomas mencionados anteriormente. Al presente, no hay ninguna contraindicación médica para ofrecer leche con hierro a infantes sanos.

Reflujo gastroesofágico es otra de las causas implicadas en cólico en los primeros meses de vida. Clínicamente, estos pacientes se despiertan irritables y lloran excesivamente, luego de 1-2 horas después de la ingestión de leche. Esto se podría documentar haciendo estudios de pH en esófago en los períodos que preceden a la irritabilidad.

Algunos han relacionado la introducción de sólidos como tratamiento para el cólico; por el contrario otros han mencionado que el uso de cereal puede ser considerado causa de cólico.<sup>19</sup> Si tomamos en consideración que en el neonato la actividad de amilasa pancreática es un 10% del valor del adulto se podría inferir el por qué algunos de estos niños podrían empeorar con el uso de sólidos. Aun así, muchos padres utilizan este método para tratar de aliviar los síntomas.

### Factores Intrínsecos y Extrínsecos

Una teoría que pretende explicar el por qué de este llanto excesivo es el sobreestímulo de estos infantes y el medio ambiente noscivo que los rodea como factores precipitantes. Algunos estudios quieren implicar la ansiedad materna como causa del problema. Hay dos maneras de ver este asunto:

- 1) la ansiedad materna como causa del cólico, o
- 2) el cólico infantil induciendo ansiedad en la madre.<sup>10</sup>

Paradise<sup>10, 20</sup> no encontró evidencia que sustentara el que un ambiente de ansiedad, hostilidad e inexperiencia materna fueran la causa de cólico en los infantes.

Carey<sup>21</sup> en un estudio prospectivo evaluó un grupo de 103 madres de las cuales 63 resultaron ser madres no ansiosas y 40 llenaban los criterios de madres ansiosas. De los 103 bebés, el 12.6% (13 pacientes) tuvieron cólico infantil. El encontró que en las madres no ansiosas hubo un 3.2% (2/63) de los bebés que tuvieron cólico. En el grupo de bebés nacidos de madres catalogadas como ansiosas encontró que un 27.5% (11/40) tuvieron cólico. Por otro lado el 72.5% (29/40) de bebés nacidos a madres ansiosas no tuvieron cólico infantil. Por lo tanto, aunque ansiedad materna puede ser un factor contribuyente importante, no es la única causa, ni la causa principal en muchos casos.

Definitivamente, los infantes pueden percibir tensión en su medio ambiente o ansiedad en la persona que los toma en brazos y es por eso que el factor ansiedad y tensión puede ser, en algunos casos, la causa, y en otros un factor contribuyente. La irritabilidad del infante puede ocasionar esta sintomatología de ansiedad y tensión excesiva y agravar o convertir en un ciclo el problema.

Otros factores envueltos en esta condición son problemas maritales: un padre ausente o extremadamente crítico, ausencia de familia extendida o de ayuda de la sociedad inmediata que rodea esa familia.

Otros autores han querido explicar el que algunos infantes tienen una exquisita sensibilidad a los estímulos externos o internos y que la respuesta a esto es el llanto excesivo e irritante. Algunos han implicado inmadurez del sistema nervioso central y otros hacen referencia a "hipertonía del infante" en donde hay un tono aumentado del músculo estriado y liso acompañado de cambios en el comportamiento, (ej), irritabilidad, hiperactividad y pobre dormir.<sup>10</sup>

Carey<sup>19</sup> nos describe como una interpretación más amplia el modelo interaccional, en donde se explica este problema de cólico infantil de una manera combinada. Existe una interacción entre estímulos externos e internos y sus respuestas o consecuencias que a su vez pueden ser la causa del cólico infantil.

Como podemos ver, hay diferentes teorías de qué es lo que causa el llamado "cólico" infantil o llanto irritable y excesivo. Probablemente, en algunos casos, haya una combinación de varios factores antes mencionados. En casos en donde no encontramos una causa orgánica que explique el síndrome, se le ha llamado llanto o cólico de causa primaria. Por el contrario, de encontrar alguna causa orgánica, se le ha llamado llanto o "cólico" de causa secundaria.<sup>19</sup>

En un intento de dirigirse hacia un tratamiento exitoso, Geertsma<sup>22</sup> encontró en su estudio dos tipos de patrones de llanto: los de "cólico clásico" y los de "llanto frecuente." También describe que los pacientes con "llanto frecuente" no reunían los criterios de la definición de cólico infantil en cuanto al número de horas de duración del llanto (cólico) y se encontró con la posibilidad de que éstos fueran excluidos del diagnóstico, (cólico infantil) aún cuando el problema causaba gran ansiedad y descontento en los padres. A estos pacientes se les privaba de un manejo apropiado para su condición.

Todo esto implica que debe haber más estudios e investigaciones respecto a este tema para así poder tener unas decisiones de tratamiento adecuadas.

### Manejo y Tratamiento (ver Tabla II)

La descripción de los episodios de cólico es importante a la vez que la frecuencia. Usualmente, estos episodios ocurren mayormente en horas tempranas de la noche o tarde en la madrugada, aunque pueden ocurrir en otros horarios.

Las acciones que toman los padres para calmar al paciente deben ser documentadas. El examen físico y repaso de sistemas debe ser negativo para cualquier causa

Tabla II

- 1- Descripción de los episodios de llanto (frecuencia, duración y el momento del día en que más ocurra)
- 2- Acciones tomadas por los padres para calmar o reducir el llanto
- 3- Examen físico y repaso de sistemas
- 4- Historial Psicosocial
- 5- Observar la relación madre-paciente en la oficina y cuarto de examen
- 6- Hacer que la madre demuestre o describa la técnica utilizada para calmar al paciente



orgánica. El historial psico-social debe ser investigado para buscar posibles factores contribuyentes, tanto en la familia como en su medio ambiente, (ej) negligencia o abuso físico.

Las observaciones del médico en la oficina son importantes ya que podríamos notar a la madre cansada, ansiosa o con coraje. Estas relaciones e interacciones madre-niño deben analizarse cuidadosamente.

El manejo y tratamiento se ha dividido en dos grandes categorías:

1. los que asumen que el dolor se origina de causas gastrointestinales.
2. los que asumen que el dolor es secundario a causas de interacción de estímulos internos y externos en el infante.

La mayoría de los que creen que el dolor es de origen gastrointestinal utilizan medicamentos como sedantes que tienen un efecto en disminuir la motilidad gastrointestinal. Donovan<sup>23</sup> no encontró mejoría significativa utilizando metilbromuro de homatropina conocida comercialmente como Sedadrops en su estudio; por el contrario, en algunos casos el número de horas de llanto aumentó luego de pasado el efecto del medicamento.

El uso de hidrocloreuro de dicitolmina, conocido comercialmente como Bentyl también fue recomendado, pero en noviembre de 1984 su uso fue excluido para infantes menores de 6 meses debido a síntomas secundarios, (ej) colapso respiratorio, apnea, convulsiones y coma,<sup>8, 10</sup> aunque estos fueron encontrados en pacientes a quienes se le administró el medicamento sin diluir.

Otros medicamentos que han sido utilizados son agentes anticolinérgicos (Colidrops) y otras drogas que contienen fenobarbital, pero éstos deben evitarse en infantes menores de 6 meses debido a sus efectos secundarios.<sup>8</sup>

Los que creen que el problema es gastrointestinal utilizan el cambio frecuente de fórmulas. Algunos autores<sup>24, 25</sup> han encontrado que este método causa un efecto negativo ya que hacemos creer a estas madres que su infante tiene verdaderamente una enfermedad o causa orgánica que provoca esta sintomatología de llanto excesivo. Barr et al<sup>26</sup> encontraron que hay poca evidencia para el cambio de leche como método terapéutico. Por otra parte están aquellos que infieren que la causa del llanto excesivo es una de interacción de estímulos internos y externos, en donde interviene tanto el temperamento del bebé y los factores externos de la familia y su medio ambiente.

Como método terapéutico, se deben utilizar las siguientes recomendaciones:

1. Debemos asegurar a la madre que éste es un infante sano y que este problema se resolverá, aunque lentamente en algunos casos.
2. Cuando el bebé esté en un ataque de llanto se debe promover el manejo sutil y suave del infante y utilizar movimientos rítmicos (ej. mecerlo en un sillón; darle un paseo en carro).<sup>27</sup>
3. Se le puede ofrecer un pacificador o bobo.
4. En todo momento, debemos evitar que el paciente coma en exceso de lo que necesita para su buen crecimiento y desarrollo.

5. Además, debemos prevenir que el infante duerma en exceso durante el día o que duerma más de tres horas consecutivas.

6. En los momentos críticos, será aconsejable que otra persona cuide del bebé para así disminuir el factor ansiedad como posible agravante.<sup>4</sup>

7. A la vez, se debe estimular el que periódicamente la madre deje a su bebé con otra persona (abuela, vecina, amiga) para así tener períodos de descanso y relajamiento y salidas fuera de la casa.

8. En los momentos en que el bebé esté dormido se debe aconsejar que la madre aproveche y descansa también, aunque reconocemos que esto es difícil si tiene otros niños y no tiene ayuda externa.<sup>8</sup>

Se ha encontrado que en sociedades<sup>8, 10</sup> en donde el bebé es llevado en un cargador al frente de la madre o en la espalda, la incidencia de este problema es mínima o inexistente, por lo tanto el uso de estos cargadores es recomendable. El cargar o coger en brazos a su bebé no lo engreirá.<sup>28</sup>

A estos bebés se les debe dar seguimiento frecuente en la oficina y en estas visitas promover el que la madre nos hable sobre sus sentimientos, sus miedos y dudas y en casos donde sea necesario y factible, la ayuda de una enfermera en salud pública sería altamente recomendable.<sup>8, 19</sup>

### Pronóstico

Esta es una condición pasajera que dura aproximadamente tres meses. En la mayoría de los casos no tendrá ninguna consecuencia para el infante y su familia.

Siempre debemos investigar la posibilidad de niño mal tratado, pues el infante con "cólico" infantil está predisposto en algunas familias a ser abusado y maltratado física y mentalmente.

**Abstract:** The literature regarding infantile colic is reviewed. It is characterized by difficulties in definition. Different theories have been implied as to its etiology: behavioral and developmental as well as gastrointestinal causes are considered.

The management and treatment based on both theories were revised. Most of them have proven to be effective in many cases.

We recognize that future research is needed so that better management and treatment can be designed and prepared for this condition.

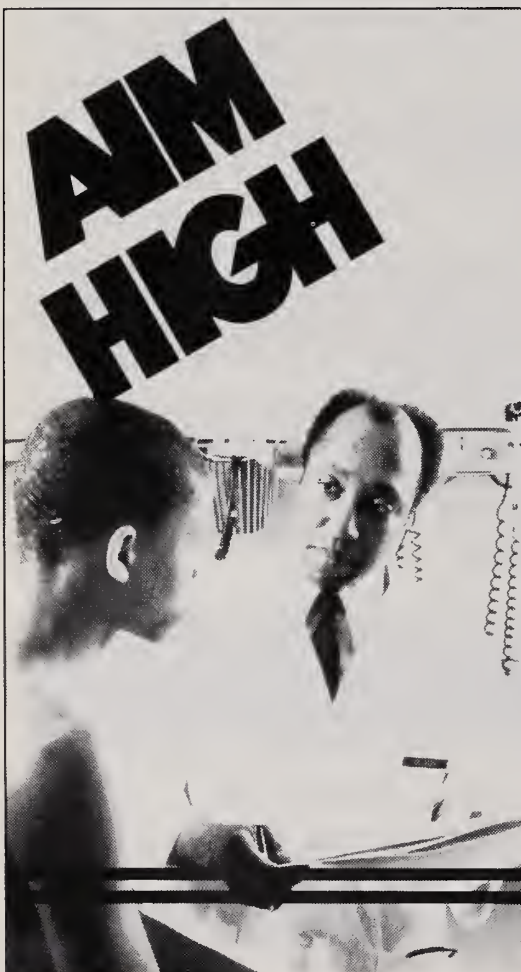
### Reconocimiento

Los autores agradecen a la Sra. Sylvia Venegas Cestero la cooperación brindada en la preparación del manuscrito.

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# SPECIAL ARTICLES

## Diabetic's Diet in the Hispanic Caribbean

Bartolomé Arce Hidalgo, MD

In the last twenty years a significant and outstanding progress has occurred in the knowledge of pathogenesis and introduction of new therapeutic methods in Diabetes Mellitus, however, the diet is still one of the most relevant issues in the treatment of this disease in any of the present types already classified.<sup>1</sup>

The diabetic diet has undergone a number of variations in its composition closely related to a better understanding of the pathogenesis of the diabetic syndrome and in the progress achieved in Nutritional Biochemistry.<sup>2</sup>

Nowadays, there is a tendency to establish an individual diabetic diet considering sex, age, nutritional stage, physical activity, type of diabetes and complications of this disease.

There is growing evidence that diabetes is linked to a metabolic impairment of nutrients and other endogenous substances, so any nutritional program concerning this disease should consider all the metabolic disorders of the patient, and the best nutritional strategy to manage these disorders.<sup>3</sup>

Another important aspect to be considered in the diabetic diet is to know which type of diabetes he is classified into. In type I diabetes this treatment should contribute to a more stable hyperglycemic control, permitting the maximum flexibility in nutritional habits and life style. On the contrary, the diet in type II diabetes is the main form of treatment as the hypocaloric diet improves insulin-resistance, the metabolic control and lipid metabolic disorders very often associated.<sup>2-6</sup>

In 1970 the results of the University Group Program for Diabetes study were published.<sup>7</sup> One of the benefits of this study was to reconsider the importance of the diet as a primary aspect in the diabetic's treatment.

Later on, in 1973 West<sup>8</sup> performed a brilliant analysis of the main causes that determine the failures of the patient's diet where the only evidence was not the relative incapacity of physicians, dietitians, and patients in order to achieve the adequate diet fulfillment, but also the lack of individuality of the diet, not considering life style, personality, dietary habits and social-economic conditions in most of the cases.

In 1975 Davidson<sup>9</sup> confirmed and emphasized West's findings stating the reasons for success and failures in the diet. He shows evidence of the health team inefficiency (physicians, nurses and dietitians) regarding the patient's nutritional education and their own incapacity to comply an adequate dietary treatment.

The purpose of this work is to analyze the diabetic diet in the Caribbean countries with hispanic influence taking Cuba as an example, to present our results and difficulties and also to demonstrate the need of a joint effort of the Caribbean countries to achieve with international support, a more adequate treatment towards our diabetic patients.

### Concept of the Hispanic Caribbean

There is no unanimous criterion about which countries are to integrate the Caribbean. On the contrary, this has been a very controversial matter that has brought about differences in the integration of the countries that should form part of it.<sup>10</sup>

The most accepted concept of Caribbean countries, is the one given by A. Dembicz<sup>11</sup> in his book "Premisas Geográficas de la Integración Socio-Económica del Caribe". He considers that this region includes all the Atlantic coast of Central America (Mexico, Belize, Guatemala, Honduras, Nicaragua, Costa Rica and Panama), the north region coast of South America (Colombia, Venezuela, Guyana, Surinam and the French Guyana), the Major Antilles (Cuba, Jamaica, Haiti, Dominican Republic and Puerto Rico), the Minor Antilles and the Bahamas.

J. Bosch<sup>12</sup> established a difference in comparison with Dembicz's hypothesis, he included El Salvador in the Caribbean area excluding Barbados and the 3 Guyanas.

Concerning the integration of the Hispanic Caribbean, Z. Wojski<sup>13</sup> established an ethno-linguistic classification considering as integrating countries, Cuba, Dominican Republic, Puerto Rico and the Caribbean coast of Colombia, Panama and Venezuela. He did not consider in this region the Caribbean coast of Costa Rica, he claimed that there were ethnic and linguistic differences in this population, in relation to the other countries.

These Hispanic Caribbean countries where we have included Costa Rica, have an ethnic formation predominantly Spaniard, but also includes Africans and American Indians. These ethnic groups more or less have

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contributed with its influence to a socio-cultural formation with common dietary habits.

The main food contribution of these ethnicities has been the following: Spaniard (porridge, soups, sausage and jerked beef); American Indian (yucca, sweet potato, guava, avocado, chayote, black and red beans and chocolate), African (malanga, yam, gumbo, plantain). All these foods have been integrated within a nutritional culture that nowadays is patrimony of the Caribbean population.

Figure 1.



Figure 1. The Hispanic Caribbean Countries.

### General Aspects of the Diabetic's Diet

One of the most important elements to consider when a diet is prescribed is to know the patient's diabetes type: Type I, type II or impaired glucose tolerance.<sup>14</sup>

In type I diabetes, insulin levels are scarce or null and usually the patient is underweight. In those cases we indicate isocaloric or hypercaloric diets together with insulin to achieve a better glycemic control.

A careful balance must be established between meals and insulin injection hours, because of the patient's inability to correct by endogenous insulin, the glycemic fluctuations determined by food intake. For this reason a strict meal timetable is necessary.

Calorie, carbohydrate, protein and fat quantities should be kept constant to maintain the balance between meals and insulin dose. Contrary of what is regularly done, it is important to plan the insulin doses related to the adequate diet.<sup>4</sup>

In type II diabetes the patients can be obese or non-obese. Cases with normal weight or underweight may be tributary as in type I diabetes, of an iso or hypercaloric diet.

In those cases with obesity, caloric restriction and weight reduction are prominent features of diet treatment.<sup>15</sup> A rigid meal plan is not necessary if daily calorie intake is strictly under control.

Finally, in cases with impaired glucose tolerance (chemical diabetes), the diet can be more flexible, and the main purpose is to limit food rich in carbohydrates, and maintain a normal weight.

Generally, the diabetic's diet must have the following characteristics:

1. Quantitative (adequate in calories)
2. Individual (specific for each patients)
3. Uniform (equal number in calories and food timetable)
4. Dynamic (adequate to the biological state of the patient: age, pregnancy, activity, associated diseases, preferences and habits)
5. Must normalize the weight and nutritional reserves and insure normal growth and development in the young diabetic<sup>16, 17</sup> (table I).

Table 1. Diabetic Diet Characterist

1. **QUANTITATIVE** (adequate in calories)
2. **INDIVIDUAL** (specific for each patient)
3. **UNIFORM** (equal number in calories and food timetable)
4. **DYNAMIC:** adequate to the biologic state of the patient (age, pregnancy, activity, associated diseases, preferences and habits)
5. **Must normalize the weight and nutritional reserves and insure normal growth and development in the young diabetic**

Considering the proportion of nutrients, evidence suggests to decrease saturated fat and cholesterol, increase fiber intake and moderate salt ingestion (specially in hypertension); allow a moderate intake of alcohol and avoid refined carbohydrate.<sup>5</sup>

### Diet Composition

#### Carbohydrates

Carbohydrate intake, as part of the dietary treatment has undergone several variation in the last years. During the first stage, United States and Western Europe prescribed low carbohydrate diets, rich in fats (similar to the population's general pattern). These diets had approximately 40% of carbohydrates, 20% of proteins and 40% of fat.

On the contrary, in Japan and the majority of the underdeveloped countries, based on traditional or economic reasons, diets with high-carbohydrate and low fat were prescribed.

In Latin America and the Caribbean, efforts were made to put in practice the Western patterns of carbohydrate restriction, however, we were right without knowing it. Some performed studies in tropical countries have demonstrated that type I and type II diabetics were satisfactorily controlled with high-carbohydrate diets.<sup>8</sup>

Later on, some published studies by Kiehm et al<sup>18</sup> and Anderson et al<sup>19</sup> in the United States ratified these previous observations. Kiehm demonstrated that the diabetic's diet with a 75% of carbohydrate, improved



diabetes control if the carbohydrates were rich in fiber.<sup>20-24</sup> Subsequently, Anderson demonstrated that diets rich in carbohydrates with a high content of complex carbohydrate also decreased cholesterol and triglycerides.

Several mechanisms have been proposed to explain the improvement of glucose tolerance with the use of diets rich in carbohydrates, among them, the induction of hepatic and gastrointestinal enzymes which regulate glucose disposal<sup>25</sup> and on the other hand, increase in the post-receptor activity of glucose metabolism.<sup>26</sup>

Nowadays, in our country we recommend diets with high carbohydrate content (55%) and with high dietary fiber, also using complex carbohydrates in the diet.

## Fat

There is no defined criterion related to quantities and fat types to be used in the diabetic's diet. The increase in carbohydrate has led to a decrease in fat content in order to maintain fixed the number of total calories;<sup>15</sup> on the other hand the increased fat intake has been related with and atherogenic effect specially linked to saturated fat and cholesterol.<sup>27</sup> These facts have clearly determined a decrease of fat content in the diabetic's diet that now goes from 20 to 35% in most countries.

Emphasis is now centered in the decrease of saturated fat and its partial substitution with monounsaturated and polyunsaturated fats.<sup>28-30</sup> Leichter et al<sup>3</sup> recommend to limit the intake of saturated fats and less than 300 mg of cholesterol.

In our country we prescribe around 30% of fat in the diet using a minimum of saturated fat and less than 300 mg of cholesterol daily. This has been achieved by using more monounsaturated and polyunsaturated fats.<sup>2</sup>

## Proteins

Protein needs in the diabetic's diet are not completely defined, however, they should be similar to the normal population, except in cases that undergo renal or gastrointestinal disorders, where the excessive protein loss must be replaced.

The American Diabetes Association<sup>31</sup> recommends a protein content in the diabetic diet between 12-20% of total calories. In our country, we are using about a 15% protein in the diet to solve daily needs.

## Dietary Fiber

Dietary fiber can be defined as the skeletal remains of plant cells that are resistant to digestion by enzymes of man.<sup>32</sup> It is mainly composed by a structural polysaccharide, cellulose; other polysaccharides as pectin mucilages and gum as well as other non carbohydrate constituents as for example, hemicellulose, pectic substances and lignin. It also has small quantities of phytic acid, silica, lipids, enzymes and raffinose.

Because of its ability to fix calcium, magnesium, zinc and iron, it has been related to the deficiencies of these ions in a population with a marginal daily intake.

Some performed studies related to the dietary fiber effects concerning carbohydrate metabolism have demonstrated that at least some types of fibers can decrease glucose levels during a tolerance test and after meals.<sup>18, 22, 33, 35</sup>

The effect of dietary fiber on glucose levels does not seem to be insulin-mediated. Although a delayed glucose absorption has been suggested, the precise mechanism by which fiber lowers blood glucose concentration remains unknown.

Concluding, diets with a high dietary fiber content could be an alternative to the use of oral agents or insulin, mainly in type II diabetes.

## Sweeteners

Sweeteners are frequently used in the diabetic's diet in a large number of countries. The main sweeteners used can be natural or synthetic. Among them saccharin, cyclamates, sorbitol, mannitol, xilitol, aspartame and fructose.

Saccharin and cyclamates are sweeteners that in some clinical researches have been related to cancer of bladder. This fact has already been refused by other studies where no carcinogenic effect has been found.

Nevertheless, in the United States saccharin intake has been limited and cyclamates usage has been forbidden. These 2 substances, besides having a high edulcorant power has no nutritional value, what makes it advantageous.

There is also a group of natural sweeteners which comprises sorbitol, xilitol and mannitol that have a caloric value similar to natural sugars. Unfortunately, sometimes they are able to determine diarrhea when they are frequently used.

In our country, we use saccharin in a limited way, basically as coffee edulcorant, but its use is indeed, very restricted. Sorbitol and mannitol are also used not as edulcorants but mostly as laxative and diuretic, respectively.

Regarding fructose it was quite in fashion in the fifties in our country, but because of its side-effects (insulin sensitivity decrease and lactic acidosis) as well as the few advantages it has compared with other sugars, its usage has been restricted.<sup>29</sup> However in some studies<sup>36</sup> a slight improvement of glycemic control has been suggested with the use of fructose.

## Specific Aspects of the Diabetic Diet.

### Applications in Cuba

The main goal of the diabetic diet must be the reestablishment of the physiologic state, an adequate physical and psychological balance; and ideal weight maintenance and the prevention of its complications.

This goal must be achieved by considering that the diet should resemble a normal one.<sup>14, 37, 38</sup>

The diabetic diet is based on the following premises:

#### 1. Percentage distribution of total calories.

We recommend the following distribution approximately:

Carbohydrates	-	±	55%
Proteins	-	±	15%
Fat	-	±	30%

We should also:

Restrict animal fat rich in saturated fats and cholesterol.

The Fatty acids should be:

Saturated	1/3
Monounsaturated	1/3
Polyunsaturated	1/3

- Use a proportion of carbohydrates mainly made of non refined sugars (polysaccharides)
- Add 40 gm of dietary fiber in the daily food intake.
- Avoid smoking definitively.

## 2. Individual diet estimate

First of all, we should estimate the patient's ideal weight. For this purpose we should use the ideal weight National Chart according to height, age and sex. Another alternative is to use Broca's formula (height in centimeters -105= ideal weight in Kg).

The percentage of the patient's present weight according to the ideal weight is estimated; if it exceeds more than a 10% of the ideal weight, the patient is considered overweight, in case he is below a 5% he is underweight. Intermediate values are considered normal. Once the ideal weight is determined, total daily intake calories can be estimated. For this purpose we multiply the patient's ideal weight by the corresponding calories of the present weight, according to the physical activity he performs (table 2).

**Table 2.**  
**Calorie Estimate according to**  
**Physical Activity and Body Weight (\*)**

		Sedent. Activity	Moder. Activity	Marked Activity
<b>Normal</b>		<b>30</b>	<b>35</b>	<b>40</b>
<b>Overweight</b>	Ideal weight	<b>20</b>	<b>25</b>	<b>30</b>
<b>Underweight</b>		<b>35</b>	<b>40</b>	<b>45</b>

(\*) The product is expressed in calories

Once the estimate of total calories is performed, they should be distributed according to the preestablished nutrient proportions (carb. 55%, prot. 15%, fat 30%) and also according to habits and food preferences of the patients.

To make possible this distribution we use a national food exchange list considering Cuban foods derived from a nutritional culture common to the Caribbean countries (table 3).

We also use official diet models with different caloric intake. The most frequently used are (1000, 1200, 1500, 1800, 2000, 2200, 2500 and 3000 calories) (table 4). These diets may undergo some necessary adjustments according to every patient's situation, by means of the exchange list.

Afterwards food is distributed in 6 timetables which includes 3 main meals, 2 snacks and supper. Timetables can be shortened according to the patient's preferences

and difficulties, however the total calory intake must be kept fixed (table 5).

Another fact to consider in type 1 diabetes is that timetables should be scheduled according to insulin administration.

Once the food distribution is scheduled we should confirm if the total food intake corresponds to the one prescribed and if carbohydrate, protein and fat proportions are approximately coincident (table 6).

**TABLA 3. LIST OF FOOD EXCHANGES**

<b>LIST 1. MILD EXCHANGE</b>		<b>LIST 3A. FRUIT EXCHANGE</b>	
Each exchange is equal to:		Each exchange is equal to:	
Carbohydrates	14 g	Carbohydrates	8 g
Proteins	7 g	Proteins	1 g
Fat	6 g	Eat	0 g
Calories	130	Calories	35
Milk, whole	1 cup 240 cc	Orange	1 moderate 100 g
Milk, evapor	1/2 cup 120 cc	MANDARIN	1 big or 2 small 100 g
Milk, powdered	3 T 30 g	Grapefruit	1/2 unit 123 g
Yogurt	1 cup 240 cc	MANGO	1/2 small 50 g
Milk, condensed	2 T 96 g	Melon	1 cup 100 g
<b>LIST 2A. VEGETABLE EXCHANGE</b>		Water melon	1 cup 150 g
Each exchange is equal to:		PAPAYA	1 cup 100 g
Carbohydrates	3 g	Banana	1 small 40 g
Proteins	2 g	MAMEY	1/4 small 50 g
Fat	0 g	Lemon juice	1/2 cup 100 g
Calories	18	Pineapple	1/3 cup 80 g
Lettuce	1 cup	CUSTARD APPLE	1/2 cup 50 g
MATERCRESS	1 cup	SOFT MASS COCONUT	1/3 c 80 g
SALT-WORT	1 cup	GUAVA	2 small 50 g
Savoy cabbage	1 cup	CHERIMOYA	1/2 moder 75 g
CERELY	1 cup	STAR APPLE	1 moderate 75 g
CHAYOTE	1 cup	SAPOTA	1 moderate 75 g
Eggplant	1 cup	<b>LIST 3B. SUGAR, PRESERVES AND ICE CREAM EXCHANGE</b>	
Coultflower	1 cup	Each exchange is equal to:	
Tomato	1 cup	Carbohydrates	12 g
Radish	1 cup	Proteins	0 g
Red pepper	1 cup	Fat	0 g
GUMBO	1/2 cup	Calories	46
French bean	1 cup	Sugar	1 T 12 g
Spinach	1 cup	Marmalade	1 T 26 g
Cabbage	1 cup	Preserves	1 T 25 g
Turnips	1 cup	Eruit paste	1 T 30 g
<b>LIST 2B.</b>		Normal ice-cream	3T 30 g
Each exchange is equal to:		Rice Custard	2 T 45 g
Carbohydrates	7 g	Custard	2 T 56 g
Proteins	2 g	Rich custard	2 T 25 g
Fat	0 g	Bread pudding	2T 52 g
Calories	30	Compote	4 T 59 g
Cooked onion	1/2 cup 100 g	Sponge cake	1/2 ox 15 g
Crude onion	1/3 cup 80 g	Gelatin dessert	1/2 cup 10 g
Bests	1/2 cup 75 g	<b>LIST 5. MEAT EXCHANGE</b>	
Carrot	2/3 cup 75 g	Each exchange is equal to:	
<b>LIST 4. BREAD, CRACKER, VIAND.</b>		Carbohydrates	1 g
CEREAL AND BEAN EXCHANGE		Proteins	7 g
Each exchange is equal to:		Eat	4 g
Carbohydrates	15 g	Calories	75
Proteins	2 g	Beef, pork, lamb, poultry, tongue,	
Fat	0 g	viscera, fish, ham	1 oz 30 g
Calories	70	Shell fish, carb, lobster	
<b>LIST 4A. BREAD AND CANCER</b>		Calamary, shrimp	1/4 cup 30 g
Boft round roll	1 unit 30 g	Egg	1 unit 50 g
Loaf	1 slice 30 g	Cottage and	
Saltine or soda		white cheese	1 oz 30 g
cracker a	4 units 30 g	Bardines	1 oz 30 g
<b>LIST 4D. VIAND</b>		Sausage, salami,	
YAM	1/3 cup 75 g	Mortadella	1 oz 30 g
MALANGA	1/3 cup 75 g	Hot dogs	1 unit
SWEET POTATO	1/3 cup 75 g	<b>LIST 6. EAT EXCHANGE</b>	
PLANTAIN	1/3 cup 75 g	Each exchange is equal to:	
YUCCA	1/3 cup 70 g	Carbohydrates	0 g
Squash	1 cup 80 g	Proteins	0 g
Potato	2/3 cup 100 g	Fat	4 g
<b>LIST 4C. CEREALS AND BEANS</b>		Calories	36
Rice	1/3 cup 70 g	Oil	1 tsp 5 g
Nounsh. paste	1/3 cup 70 g	Fat	1 tsp 5 g
Flour	1/3 cup 66 g	Butter 1 tsp	5 g
Oats	5 T 120 g	Mayonnaise	1 tsp 5 g
Corn flakes	3/4 cup 18 g	Cream cheese	2 tsp
Rice cream	2 T 15 g	Bacon	1 small slice 15 g
Milky flour	5 T 28 g	Peanut	15 units
Roasted corn meal	2 T 60 g	Avocado (small)	1/4 slice 50 g
PEAS	1/4 cup 60 g		
BLACK BEANS	1/4 cup 60 g		
RED BEANS	1/4 cup 60 g		
CHICK PEAS	1/4 cup 60 g		
LENTIL	1/4 cup 60 g		
STRING BEAN	1/4 cup 60 g		



Table 4.

PUBLIC HEALTH MINISTRY NATIONAL INSTITUTE OF ENDOCRINOLOGY AND METABOLISM																													
Name: Vivian Cardoso	Age: 30																												
Real weight: 62 kg	Medical history: 5903056623																												
Ideal weight: 57 kg	Data: 07/07/89																												
Height: 162 cm																													
This diet has about 1800 calories																													
Carbohydrates: 241 g (34%)																													
Proteins: 312 g (17%)																													
Fat: 513 g (29%)																													
<table border="1"> <thead> <tr> <th>BREAKFAST</th> <th>LUNCH</th> <th>DINNER</th> </tr> </thead> <tbody> <tr> <td>1 c milk</td> <td>2 oz chicken in juice</td> <td>2 oz fish minced</td> </tr> <tr> <td>1 roll</td> <td>1 boiled potato</td> <td>1 c squash</td> </tr> <tr> <td>1 tsp butter</td> <td>6 T red beans</td> <td>9 T rice and beans (congrì)</td> </tr> <tr> <td>1 boiled egg</td> <td>6 T rice</td> <td>1 roll</td> </tr> <tr> <td></td> <td>1 c lettuce and tomato salad</td> <td>1 c cabbage and carrot salad</td> </tr> <tr> <td></td> <td></td> <td>2 tsp olive oil</td> </tr> <tr> <td>SNACK</td> <td>SNACK</td> <td>SUPPER</td> </tr> <tr> <td>1 C orange juice</td> <td>2 bananas</td> <td>1 c yogurt</td> </tr> </tbody> </table>			BREAKFAST	LUNCH	DINNER	1 c milk	2 oz chicken in juice	2 oz fish minced	1 roll	1 boiled potato	1 c squash	1 tsp butter	6 T red beans	9 T rice and beans (congrì)	1 boiled egg	6 T rice	1 roll		1 c lettuce and tomato salad	1 c cabbage and carrot salad			2 tsp olive oil	SNACK	SNACK	SUPPER	1 C orange juice	2 bananas	1 c yogurt
BREAKFAST	LUNCH	DINNER																											
1 c milk	2 oz chicken in juice	2 oz fish minced																											
1 roll	1 boiled potato	1 c squash																											
1 tsp butter	6 T red beans	9 T rice and beans (congrì)																											
1 boiled egg	6 T rice	1 roll																											
	1 c lettuce and tomato salad	1 c cabbage and carrot salad																											
		2 tsp olive oil																											
SNACK	SNACK	SUPPER																											
1 C orange juice	2 bananas	1 c yogurt																											

Notes: This is a daily menu example. Food choice is according to exchange list.

Diet of 1500 calories: 206g Carb (55%), 56g Protein (15%), 50g Fat (30%)

	BREAKFAST	Snack	LUNCH	Snack	DINNER	Supper
List 1 Milk	1	0	0	0	0	1
List 2a Veg.	0	0	1	0	1	0
List 2b Veg.	0	0	1	0	1	0
List 3a Fruits	0	2	2	2	2	0
List 3b Desserts	0	0	0	0	0	0
List 4a Bread						
and Cereals	1	0	0	0	0	1
List 4b Viands	0	0	1	0	1	0
List 4c Rice						
and Beans	0	0	1	0	1	0
List 5 Meat	0	0	2	0	2	0
List 6 Fat	2	0	1	0	1	0

Table 6.

### Diet Verification: Reality vs Proposed

Digt of 1500 calories 206 g Carb.55%, 55g Proteins 15% 50g Fat 30%

	Exchanges	Carboh.	Prot.	Fat	Calories
List 1 Milk	2	20	14	12	260
List 2a Veg.	2	6	4	0	36
List 2b Veg.	2	14	4	0	60
List 3a Fruits	2	64	8	0	200
List 4a Bread	2	30	4	0	140
List 4b Viands	2	30	4	0	140
List 4c Rice Beans	2	30	4	0	140
List 5 Meat	4	4	20	16	300
List 6 Fat	4	0	0	16	144
Total g.		206	70	44	1500
Calories		824	200	396	1500
Real Percentage		55%	19%	26%	100%

In cases of patients who have difficulties in learning to manage the exchange list because of cultural reasons, or in some cases where the nutritional program starts, we use another type of diet with a planned weekly menu. Table 7 shows an example of this menu. In a food survey performed in diabetics in a health area, we found a greater acceptability of the weekly menu in comparison

TABLE 7.  
Diet of 1500 cal. 20 bg Carb. (50%), 56g Prot. (15%), 50g Fat (30%)

Monday	Tuesday	Mednesday	Thursday
<b>BREAKFAST</b>	<b>BREAKFAST</b>	<b>BREAKFAST</b>	<b>BREAKFAST</b>
1 c milk 1 roll 2 tap butter	1 c milk 1 soft roll 2 tap butter	1 c yogurt 4 saltine crackers 2 tap cream cheese	1 c milk 1 soft roll 1 tap olive oil
<b>SNACK</b>	<b>SNACK</b>	<b>SNACK</b>	<b>SNACK</b>
2 bananas	2 oranges	1 small MANGO	1 CUSTARD APPLE
<b>LUNCH</b>	<b>LUNCH</b>	<b>LUNCH</b>	<b>LUNCH</b>
2 oz roast fish 1 tap beans 2 tap rice 1/3 c boiled plantain cc cabbage-carrot salad tsp olive oil pineapple (Sca)	2 oz has sined 2 T rice 1/3 c boiled sweet potato 1 c tomato, lettuce and onion salad 1 tsp olive oil 1 small MANGO	2 oz chicken in juice 3 T rice 1/3 c boiled YUCCA 1 c GUMBO and carrot salad 1 tsp olive oil 1 grapefruit	2 T beefmied fish 3 T corn flour 1/4 boiled SWEET POTATO 1 c cucumber beets salad 1 tsp olive oil 2 small bananas
<b>SNACK</b>	<b>SNACK</b>	<b>SNACK</b>	<b>SNACK</b>
1 c orange juice	2 bananas	4 MANDARINS	1 grapefruit
<b>DINNER</b>	<b>DINNER</b>	<b>DINNER</b>	<b>DINNER</b>
2 oz beefsteak 3 T RICE AND BEANS (CONGRIL) 1 boiled potato 1 T lettuce and tomato salad 1 tsp olive oil 1/2 small MAMEY	2 boiled eggs 1 T rice 1 boiled potato 1 tap olive oil 1 c cabbage and red pepper salad	2 oz roast fish 1/2 c noodle soup 1/3 c MALANGA 1c french beans and beets salad 1 tsp olive oil 2 small bananas	2 oz ham 2 T rice 1 T LENTIL 1 boiled potato 1 c lettuce and carrot salad 1 tsp olive oil 1/2 small MAMMEY
<b>SUPPER</b>	<b>SUPPER</b>	<b>SUPPER</b>	<b>SUPPER</b>
1 c yogurt 4 small soda crack	1 c milk 4 small salt. crack	1 c milk 4 small soda crack	1 c yogurt 4 small salt. crack
Coffee and tea can be drunk as pleased, but without sugar. (oz=ounce; T=tablespoon; tsp=teaspoon; c=cup)			
<b>BREAKFAST</b>	<b>BREAKFAST</b>	<b>BREAKFAST</b>	<b>BREAKFAST</b>
1 c yogurt 4 saltine crackers 2 tsp mayonnaise	1 c milk 1 roll 2 tsp butter	1 c yogurt 4 small soda crack 2 tsp cream cheese	
<b>SNACK</b>	<b>SNACK</b>	<b>SNACK</b>	<b>SNACK</b>
2 1 tsp butter 1 c cabbage and red pepper salad 1 c fruit cocktail PAPAYA, MANGO, pineapple and water melon	1 tomato and red pepper salad 1 tsp olive oil 2 small bananas	MALANGA 1 tsp olive oil 1 c french beans and red pepper 1 small CHERIMOYA	
<b>SNACK</b>	<b>SNACK</b>	<b>SNACK</b>	<b>SNACK</b>
2 bananas	1 medium CHERIMOYA	2 c PAPAYA	
<b>DINNER</b>	<b>DINNER</b>	<b>DINNER</b>	<b>DINNER</b>
2 oz roast chicken 1/2 c noodle soup 1/3 c SMASHED PLANTAIN 1 c lettuce, CHAYOTE and red pepper salad 1 tsp olive oil 1 round slice pineapple (5cm)	2 oz ham 1 T chickpea 2 T rice 1/3 c boiled YUCCA 1 c watercress and carrot 1 tsp olive oil 1 CUSTARD APPLE	2 oz meat with STEWE EGGPLANT 3 T rice 1 boiled potato 1/2 tomato and cucumber salad 1 tsp olive oil 2 small bananas	
<b>SUPPER</b>	<b>SUPPER</b>	<b>SUPPER</b>	<b>SUPPER</b>
1 c milk 1 soft roll	1 c milk 4 small salt. crack	1 c yogurt 1 soft roll	
Coffee and tea can be drunk as pleased, but without sugar. (oz=ounce; T=tablespoon; tsp=teaspoon; c=cup)			

to those which use the exchange list, not well managed by doctors and patients.

Finally, for research studies in hospitalized patients, we use a special model which allows to verify the exact calories and nutrients of the daily intake. With this model we can exactly check the total calories offered to the patient and the debris left. The difference is the exact quantity of food eaten (Table 8).

TABLE 8

PUBLIC HEALTH MINISTRY ENDOCRINOLOGY				DIET QUANTITATIVE CONTROL								MEDICAL HISTORY 64042403379						
UNIT "Hospital H. Aneijeiras"																		
SURNAME 1 García		SURNAME 2 Pérez		NAME Martha								PED SI						
DAY	MONTH	YEAR	INDICATED DIET: 1500 calories								INDICATED NUTRIENTS							
03	07	89	MILK	VEG.	FRUIT	BREAD	VIAND	RICE	BEANS	MEAT	FAT	CARD.	PROT.	FAT	CAL.			
BREAKFAST			240			30				60	5	30	16	18	320			
SNACK					200							16	2	0	70			
LUNCH				130		30	75	60	60	60	5	62	22	15	475			
SNACK					100							8	1	0	38			
DINNER				150		30		40	60	40	5	57	24	15	453			
SUPPER			240			30						29	9	6	200			
DAY	MONTH	YEAR	INDICATED DIET: 1500 calories								TOTAL		202 74 1533					
03	07	89	MILK	VEG.	FRUIT	BREAD	VIAND	RICE	BEANS	MEAT	FAT	CARD.	PROT.	FAT	CAL.			
BREAKFAST			240			30				30	5	30	16	10	320			
SNACK					200							16	2	0	70			
LUNCH				200		30	80	60	60	60	5	62	22	15	475			
SNACK					100							8	1	0	35			
DINNER				150		30		40	60	60	5	55	21	12	400			
SUPPER			240			30						29	9	6	200			
Total												200 71 43 1500						

### Health Organization in Cuba and Diabetic's Diet Education

Our health system considers Diabetes Mellitus as a main problem of health. In some studies performed in our country, we have found a diabetes morbidity of 3.8%.<sup>39, 40, 41</sup>

These results have contributed to the development of Endocrinology in our country as the main force regarding medical attention in diabetes.

Today we have a National Institute of Endocrinology, 13 Endocrinology Departments in Havana and one Endocrinology Department in each of the 14 provinces of the country.

We also have 3 special centers in Havana, Camagüey and Santiago de Cuba for specific medical care of the diabetic population. There are 11 summer vacational camps for diabetic children all over the country (Fig. 2).

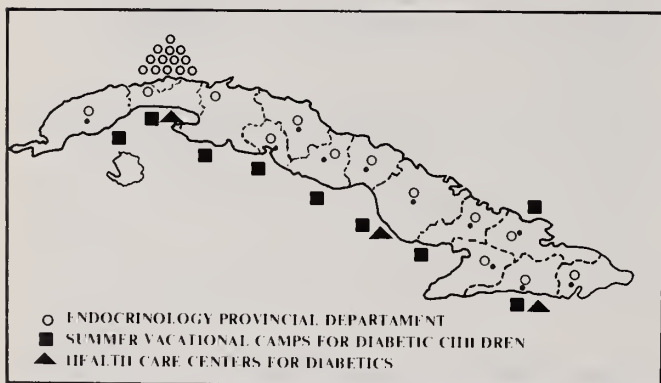


Figure 2. Health organizations of diabetics in Cuba.

In the National Institute of Endocrinology and Hospital "Hermanos Ameijeiras", national courses on diabetes are offered for all specialists of the country. These courses are complemented with other provincial courses.

All this organization is considerably important in the prevention and treatment of Diabetes Mellitus where diabetic education plays a significant role. To achieve this goal, in the programmed courses for physicians and patients, the staff of lecturers is formed by endocrinologists, nurses, physical education professors, health educators and dietitians who are in charge of training physicians and patients in the management of the diet.

The incorporation of the family physicians to the primary level of the Health System, has enabled us to widen the medical care to the diabetic population. For that purpose we have organized courses for family physicians and their nurses where the dietitian plays an important role concerning the diet management. We have also supply the family physician with diet models and exchange lists to help the patient in the management of the diet.

Annually, we organize on television a number of talks offered by specialize teams which also includes the management of the diabetic's diet, together with booklets on diabetic education.

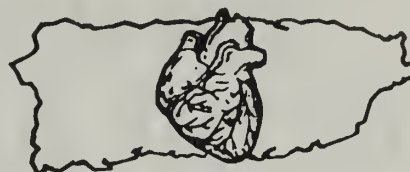
Finally, we consider that this even can be the starting point to promote a united effort of all the Caribbean countries with similar ethnic cultural and nutritional background, in order to organize the optimal assistance to the diabetic patient in this region.

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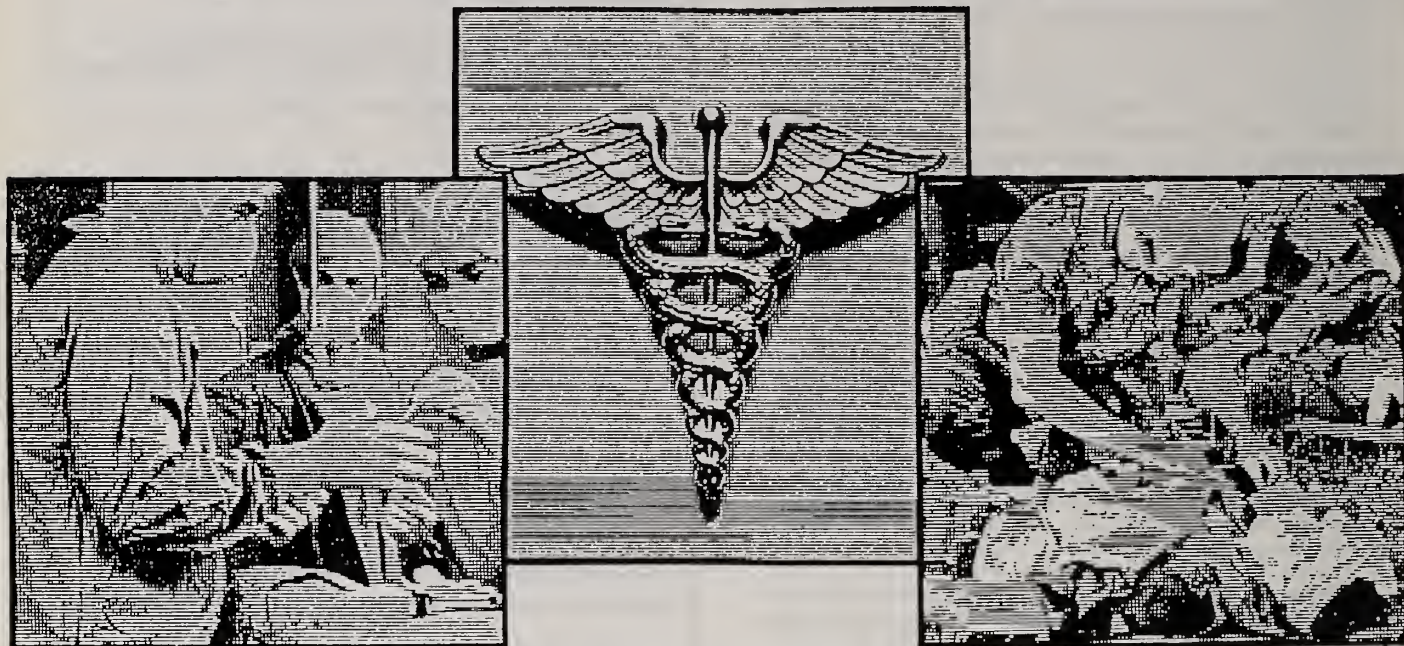
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# Truncated Opportunities No-Place for Serendipity

Enrique Vázquez-Quintana, MD, FACS\*

It has been stated that clinical and research observation need to happen to the prepared mind. Some important discoveries have been made by chance or serendipity. The word serendipity originated from the name Serendip. Serendip was the old name of Ceylon, the modern name of Ceylon is Sri Lanka. The word was coined in the 18th century by Horace Walpole, an English writer in his tale "The Three Princes of Serendip". It is said that many years ago the princes started a journey around the country and were surprised by the things they found and which they were not aware existed in their nation. To be of lasting value such serendipitous discoveries must be followed up and exploited fully or they will remain mere marginal notes to history.

Immediately following the foundation of the University of Puerto Rico School of Medicine an Experimental Surgical Laboratory was established. Besides being the proper and unique setting for the initial exposure of medical students to the aseptic techniques and the proper behavior in the operating room, the facilities were used for research in Surgery. Since then many research projects have been conducted by medical students, surgical residents and faculty members. To this date, this dual role has been maintained. Initially, in many instances the significance of the research was not appreciated, either locally or nationally.

At least five projects come readily to my mind, as examples of these frustrating circumstances, which were presented at surgical meetings or published both locally and nationally but to which no follow up studies were conducted by various reasons.

1) In 1956 Dr. Gumersindo Blanco, Dr. Alberto Adams and Mr. A. Fernández published an article entitled "A Direct Approach to the Aortic Valve: II, Acute Retroperfusion of the coronary sinus."<sup>1</sup> Although this technique was used clinically that same year it laid dormant for many years. Recently, the use of retrograde perfusion of the coronary sinus has been reintroduced with success.<sup>2</sup>

2) In 1958 Dr. Gumersindo Blanco, Dr. David Rodríguez Pérez, Dr. Alberto Adams and Mr. A. Fernández conducted important experimentation on heart and lung transplantation, describing the surgical technique for such procedure. It was probably one of the very first studies on that matter. At that time the importance of this piece of research was not recognized and further developments in this area had to await for a better understanding

of the immunologic system. Their findings were published in Archives of Surgery in 1958.<sup>3</sup> Twenty years transpired before it could be employed in humans.

3) In 1958 in an outstanding piece of work Mr. Natividad Gómez, a laboratory technician, working at the time at our Surgical Research Laboratory developed a technique of internal mammary to coronary artery anastomosis in dogs on a beating heart and without the cardiopulmonary by-pass machine.<sup>4</sup> This research was pursued further by Dr. Milton L. Cullen, Dr. Gumersindo Blanco, Dr. Luis E. Nuñez, Dr. Etanislav Rey-Baltar and Charles P. Bailey in Philadelphia. They published their successful results in October 1958 in the Journal of the Albert Einstein Medical Center.<sup>5</sup> Nowadays this procedure (performed during cardiopulmonary by-pass and using hypothermia with cardioplegia) is one of the most frequently employed in cardiac surgery.

4) In 1967 Dr. Leo Cuello, Dr. Enrique Vázquez Quintana, Dr. Brígido Berrios, Dr. Víctor S. Gutiérrez and Frank L. Raffucci published their research findings on the use of "Peritoneal Dialysis in Acute Pancreatitis in Dogs."<sup>6</sup> A better survival was documented using this technique in dogs in which pancreatitis was produced by ligating the pancreatic ducts and injecting autologous bile in the major pancreatic duct.

The method was never tested in humans due to discrepancies in the accurate diagnosis and selection of patients with hemorrhagic pancreatitis. No further studies were conducted and eventually other investigators developed the severity of disease criteria for acute hemorrhagic pancreatitis.

5) In 1967 Dr. Leo Cuello, Dr. Enrique Vázquez Quintana, Dr. Rosendo Ríos, Dr. Frank L. Raffucci and Mr. Víctor Pérez Cintrón published their clinical results on the use of "Autologous Blood Transfusion in Thoracic and Cardiovascular Surgery".<sup>7, 8</sup> The benefits and advantages of using autologous blood were firmly established. Nevertheless this modality of blood utilization was not exploited. Based on the fact that our blood Bank lacks the basic logistics for blood drawing, storage and preserving the blood for the actual donor this method has not gained wide acceptance. Nowadays the autologous blood transfusion modality must have a wider utilization based on the possible prevention of the transmission of hepatitis and AIDS. Today the method is employed in many cardiac surgery services.

Similarly research in liver disease and hemodialysis was conducted at the Surgical Research Laboratory of our School of Medicine. In fact the first hemodialysis machine was utilized in dogs in the Surgical Research Laboratory. The Surgical Laboratory now carries the name of Dr. Frank L. Raffucci, the mentor and intel-

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lectual father of many of the surgeons practicing and teaching surgery in Puerto Rico.

But what are the reasons for the interruption or discontinuation of the lines of surgical research previously established in our School of Medicine? In my opinion they are as follows:

1. Research funds have diminished and the procurement of funds is more competitive. Mainland academic centers occupy a privileged position in this regard.
2. In general our institution is not as competitive as similar academic centers in the United States.
3. We lack the required infra-structure needed to conduct basic research as compared to clinical research.
4. Because of the knowledge explosion research is more sophisticated and requires specific training in research techniques.
5. Low faculty salaries have led potential investigators to engage in outside practices that barely permit them to survive economically.
6. Bureaucratic problems delaying the acquisition of the needed materials and animals at times exasperate the most dedicated investigator.
7. Funds assigned to the Surgical Research Laboratory are insufficient to pay for the ancillary personnel needed for research.

The reasons enumerated above prevent the conduction of a significant number of research projects. The Accrediting agencies cite this as an area of concern in almost all the programs evaluated, both undergraduate and graduate. In order to be competitive we have to correct the deficiencies mentioned above to prevent further erosion of our training and educational efforts, but I feel the bottom line is money.

I suspect other institutions or individual investigators have had a similar experience, in not having exhausted a promising line of research.

In a sense serendipity has been betrayed.

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## Sirviendo al Pueblo y a la Profesión Médica



ASOCIACION MEDICA DE PUERTO RICO





# MEDICAL ASPECTS OF NUTRITION

## A Study on Diet, Nutrition and Disease in the People's Republic of China Part II\*

T. Colin Campbell, PhD.\*\*

As previously summarized, an unusually comprehensive array of life and death characteristics was recorded for the diet and disease study in the People's Republic of China, including information about known nutrients and mortality rates for more than four dozen diseases and aggregate disease groups. Before commenting on some of the observations in this study, it is important to understand the research philosophy that should guide interpretation. When each characteristic is compared to the remaining characteristics, more than 9,000 statistically significant correlations are produced. However, the task remains to decide which ones are chance observations with no biological meaning and which ones are biologically plausible. None of these statistically significant associations alone prove causality; they only provide evidence which, when combined with other information, may indicate real biology. Thus, these various statistically significant associations require interpretation from the biological perspective. The statistical perspective can only serve as a guide within the context of biological common sense. Such interpretation, while subjected to the process of critical questioning, must also be imaginative. The following, therefore, represents a small sample of the observations obtained thus far from the China data.

### Plasma Cholesterol and Coronary Heart Disease

Plasma cholesterol is much lower in China (88-165mg/dL) than in the U.S. (155-274 mg/dL) and other Western countries. Risk of coronary heart disease (CHD) declines about 2%-3% for each 1% decline in plasma cholesterol within range of cholesterol levels in the U.S. This relationship, however, is not particularly clear at cholesterol levels within the lower range, not only for CHD but for other disease as well. For example, in a study of

American men of Japanese ancestry living in Hawaii, some evidence indicates that total mortality, especially for colon cancer, increases at plasma cholesterol levels below about 180 mg/dL.

Other evidence, however, suggests that this inverse relationship may be explained as an experimental artifact caused by an effect of the disease on plasma cholesterol rather than the reverse.<sup>2</sup> In contrast, the China data offer an opportunity to examine these relationships not only at lower cholesterol levels but also for healthy individuals. CHD risk in China continues to decline to an almost negligible level when plasma cholesterol levels are low. Moreover, colon cancer mortality also decreases with lower cholesterol levels ( $r=0.44$ ,  $p<0.001$ ). This range of cholesterol, extending below that traditionally seen among Western populations, offers a unique opportunity to examine the consequences of risk for various diseases.

### Fiber Intake and Colon Cancer

A current topical issue is the relationship between large-bowel cancer and dietary fiber intake. In the China study, only 49 of the 5 counties distinguished colon cancer from rectal cancer while the other 16 counties combined these rates. Mean dietary fiber intake in China (33g/day) was observed to be three times greater than that of the U.S. (11g/day) and ranging as high as 77g/day. The intakes of several individuals fiber fractions, including total dietary fiber, total neutral detergent fiber, hemicellulose, cellulose, lignins, cutins, pectin and six soluble fiber fractions characterized by various monosaccharide residues (rhamnose, fucose, arabinose, xylose, mannose and galactose), were measured. Intakes of most of these fractions were highly correlated with each other and thus far, associations of large-bowel cancer risk with individual fiber fractions cannot be distinguished. When compared to other countries, the China data lend support to the dietary fiber-large bowel cancer hypothesis because fiber intakes are relatively high while large-bowel cancer mortality rates are relatively low. However, within these unusual Chinese (low prevalence of large-bowel cancer, high dietary fiber intake), large-bowel cancer was

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inversely correlated with each of the fiber fractions but the correlations generally were not statistically significant. Thus, while these data support the general hypothesis of high fiber intake and low mortality rates for large-bowel cancer, they do not provide more definitive information on individual fiber fractions.

### Iron Status

Mean iron intake in China (34.4 g/day) is almost twice that of the U.S. (18.4 g/day), with most of the iron in China coming from nonheme plant sources. Furthermore, iron status among Chinese adults appears to be adequate with virtually no evidence of anemia, though anemia among children and pregnant mothers was not measured. At first inspection, it appears that iron status is not compromised, irregardless that the nonheme plant iron may be less absorbable than heme iron, based on evidence from experimental studies in animals and metabolic studies in humans.

### Energy Intake

The intakes of fat, carbohydrate and protein in China substantially differ from those in Western countries. Energy intake is approximately 20% higher in China than in the U.S. when body weight is taken into consideration. This observation may be somewhat surprising for many readers, especially when the fear of famine and food shortage seems to have been so much a part of past Western literature. A major famine did occur in China around 1960 and areas of inadequate energy intake have been known to exist during more recent decades. However, the 1983 survey revealed that mean energy intake was more than adequate in virtually all 65 counties. This was corroborated by a similar observation drawn from a 1982 survey of 280 counties.<sup>3</sup> Such affirmations do not, of course, exclude the possibility that insufficient intakes may continue to persist, particularly for children, in some of the more remote areas.

A high mean energy intake is also of interest when compared to the low prevalence of obesity and obesity-related disease in China. For example, mean body mass (weight/height<sup>2</sup>) is 20.5 in China but 25.8 for a comparable adult male in the U.S. Thus, the higher energy intake and lower prevalence of obesity in China provide a provocative opportunity to investigate this well-studied relationship from a different perspective. Factors, such as amount of physical activity, dietary composition, genetic differences, long-term adaptation to a very different dietary lifestyle and early life dietary habits, have to be evaluated before conclusions can be drawn. However, it would appear possible that the physical activity level of the Chinese could account, at least in part, for the low prevalence of obesity, although no measure of physical activity was recorded in this survey. Theoretically, the effects of low fat and low protein consumption (though lower efficiency of energy utilization) may help to prevent the development of obesity.

### Menarchal Age

Age at menarche is markedly delayed among young Chinese women, ranging from 15.2 to 18.9 years. Mean

menarchal age in the U.S. is around 12 years. The significance of this observation may be quite profound both in reference to nutritional status and to cancers of the reproductive organs later in life. Age at menarche is closely coupled with early life nutrition. Diets rich in energy, protein, calcium, fat and other growth-stimulating factors, when consumed by the sexually immature youth, enhance the rate of growth, causing earlier onset of menarche.<sup>4</sup> Unfortunately, this type of response is also related to a higher risk of breast cancer later in life. On this basis, therefore, the maximum rate of growth during early life may not be desirable.

### Aflatoxin Ingestion

Aflatoxin, a mold toxin produced by the growth of *Aspergillus flavus* upon certain improperly harvested and stored foods such as corn, peanuts and sweet potatoes, is generally regarded as one of the most potent of all chemical carcinogens, causing primary liver cancer in certain laboratory animal species. Discovered in 1961,<sup>5</sup> this toxic material has engendered much interest among people working in areas of food commerce, government regulation of chemical carcinogens and health policy because small amounts of aflatoxin residue have often been found on certain foods in the marketplace. In 1987, the International Agency for Research on Cancer, a World Health Organization laboratory, convened an expert panel who concluded there was "sufficient evidence that aflatoxin is a probable human carcinogen." The numerous human studies on aflatoxin and primary liver cancer that support this conclusion were undertaken without consideration of the more profound liver cancer risk factor, persistent infection with hepatitis B virus.<sup>6</sup> The China study represented the most comprehensive and statistically sensitive study on aflatoxin, hepatitis B virus and primary liver cancer ever performed and the data obtained showed no relationship between aflatoxin exposure and primary liver cancer. In contrast, persistent infection with hepatitis B virus, as indicated by active viremia, was highly significantly correlated ( $p < 0.001$ ) with primary liver cancer.

### Disease Complexities

One of the original objectives of this study was to investigate the causes of disease within the context of biological complexity, namely, a) that most diseases have multiple causes b) that specific causes may affect more than one disease and c) that various causes interact with one another to produce disease. Therefore, an investigation was carried out to determine a) if individual diseases had a tendency to cluster into groups and b) whether or not such groups had a tendency to share common causes. Examination of a matrix of correlation coefficients comparing each disease mortality rate to every other disease mortality rate showed that there were two large groups of disease, meaning that diseases within each group shared similar geographic patterns. One group included communicable diseases while the second contained chronic degenerative diseases (cancers, heart disease, diabetes). The communicable disease group was associated ( $p < 0.001$ ) with agricultural activity, lower



income and more illiteracy while the other was correlated ( $p < 0.01$ ) with industrial development, and greater income and literacy. In other words, the communicable disease group is found in areas more prone to poverty while the chronic degenerative disease group is observed in areas with more socioeconomic affluence.

Sharing of common geographic patterns by each group of diseases implies a sharing of common causes. This question was investigated by creation of a single index of each disease group for each survey county, then comparing these indices with various dietary, nutritional and life-style characteristics. Diseases of poverty were correlated with lower hemoglobin levels, shorter body height, lower body weight, more urinary chloride and less tissue riboflavin repletion. Diseases of affluence were characterized by greater body height and body weight, higher plasma cholesterol and more plasma albumin. When these various relationships are considered collectively, a diet low in protein, fat and salt, but sufficient to allow for adequate synthesis of hemoglobin, should be associated with relatively low mortality rates for both disease groups.

This type of analysis also provides information about the dietary and lifestyle conditions that influence the epidemiological transition from diseases of poverty to diseases of affluence known to occur with economic development. When all of the dietary and nutritional factors were considered comprehensively and statistically analyzed by factor analysis, it was possible to identify those factors that might influence the development of diseases of affluence. This analysis indicated that a diet rich in protein, particularly animal protein, may have the greatest potential for enhancing risk for these diseases. This statistically significant observation is more remarkable because total and animal protein intakes in China are relatively low when compared to the U.S. Comparable data for China and the U.S. (for a reference adult male) show that total protein intake is 66g/day and 94g/day with each diet including 7% and 70% animal protein, respectively. With the exception of a few

nomadic nationalities in northern and western China, the range of mean total protein intake for the 65 survey counties was 49-91 g/day and 0%-20% animal protein. Given that a statistically significant effect of protein nutrition was observed at this relatively low level of intake, it is possible that a range also including U.S. intake would produce an even more striking result. This finding suggests that a diet that minimizes the intake of animal food might optimize reduction of both types of disease simultaneously, if the remaining plant foods are varied and of high quality.

### Conclusion

This brief review presents some of the more obvious relationships so far discovered in the China data base. Most will be more fully developed elsewhere. In several instances, these findings lead to interpretations that require further evidence and substantiation before firm advice can be formulated. However, this is the central feature of the data base, namely, that it represents a different perspective on diet and disease relationships than previously available from surveys of Western subjects. And, as such, it is hoped that these data, especially when coupled to more detailed information now being gathered, will stimulate rational discussion of issues to provide knowledge that is mutually beneficial for all peoples, regardless of their nationalities.

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# COMENTARIO

## Cuidado Preconcepcional

Edward O'Neill, MD\*

**H**a habido mejoría en la morbilidad y mortalidad materna y perinatal, pero ésta última se ha estancado en los últimos cinco años. Factores responsables por esta mejoría están entre otros:

1. Antibióticos
2. Sangre y sus derivados
3. Vacunaciones efectivas
4. Rhogam
5. Mejor cuidado perinatal
6. Más facilidades para diagnósticos:
  - A) Sonograma
  - B) Amniocentesis genética y no genética
  - C) Alfa-fetoproteína
  - D) Biopsia de la vellosidad coriónica
  - E) Monitoreo electrónico auditivo
  - F) Velocidad del flujo sanguíneo a través del cordón
  - G) Gases arteriales
7. Intensivos neonatales
8. Reconocimiento de embarazo de alto riesgo
9. Subespecialistas de medicina materna/fetal y neonatología
10. Tratamiento intrauterino del feto
11. Transporte intrauterino

Para reducir más la morbilidad materna y perinatal es necesario el establecer el cuidado preconcepcional, ejemplo en la madre diabética donde se ha demostrado una menor incidencia de anomalías congénitas cuando la diabetes ha estado controlada usando la hemoglobina glicosilada como parámetro.

Se deben establecer clínicas para cuidado preconcepcional en los hospitales del estado y municipio. En el Hospital Municipal de San Juan se ha establecido una. Los compañeros en la práctica privada deben ofrecer ese cuidado en su oficina. Candidatos a estas clínicas son pacientes de alto riesgo como:

- A) Diabéticas
- B) Defectos del tubo neural
- C) Hipertensas
- D) Cardíacas
- E) Obesas
- F) Malnutridas
- G) Drogadictas
- H) Tomadoras de alcohol y fumadoras
- I) Empleo de alto riesgo
- J) Abortos repetidos
- K) Otros

Con el control preconcepcional de estas condiciones se reducirá la incidencia de enfermedades congénitas y se reducirá la mortalidad y morbilidad, antenatal, intra-parto y neonatal.

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# CARTAS AL EDITOR

## Un Buen Servicio Organizado de Control del Dolor Agudo y Crónico; ¿Por qué no lo Logramos en Puerto Rico?

**E**n el pasado y aún en el presente en Puerto Rico la participación del anestesiólogo y enfermera anestesista con el paciente obstétrico se limitaba al momento del nacimiento mismo. Durante el trabajo del parto, que comprende desde que se inician los dolores de parto hasta que ocurre la dilatación completa de cervix, la analgesia estaba a cargo del obstetra. El tiempo usual del trabajo de parto varía mucho por intervenir muchos factores. El parto vaginal en sí, i.e., el nacimiento, usualmente es corto y el cuidado del anestesiólogo no se extiende a más de una hora.

En Puerto Rico, durante los últimos años por múltiples razones se ha utilizado el método psicoprofiláctico o de parto sin dolor. Este método sin embargo no ofrece en algunas pacientes suficiente disminución del dolor lo cual hace necesario proveerle al paciente otras alternativas para evitar el sufrimiento de la futura madre durante el parto y el *trauma psicológico* que éste puede ocasionar además de las posibles complicaciones.

En el presente está disponible una técnica anestésica que un obstetra o anestesiólogo entrenado pueden utilizar en estos pacientes. La anestesia epidural para controlar los dolores del trabajo de parto representa un gran progreso en la anestesia obstétrica para beneficio de estos

pacientes. Esta técnica también está siendo utilizada en el control del dolor post operatorio y el dolor crónico. Los estudios hechos con relación a los resultados y beneficios marginales de esta técnica han demostrado una disminución en la morbilidad post operatoria y la estadía de los pacientes quirúrgicos, lo cual beneficia tanto los seguros médicos que compensan al hospital a base de *per diem* como el hospital, cuando son compensados a base de DRG's.

Recomendamos por lo tanto que los seguros médicos locales reconozcan este progreso en la anestesia obstétrica y en el control de dolor post operatorio y dolor crónico estableciendo un método de pago razonable por estos servicios adicionales del anestesiólogo (o del obstetra) entrenado en esta técnica y que esté dispuesto a asumir la responsabilidad en el caso de epidurales para el control de dolor del trabajo del parto, del dolor agudo post operatorio y el dolor crónico.

Todo hospital moderno debe ofrecer para sus pacientes un servicio organizado de control del dolor post operatorio, obstétrico y del dolor crónico. No hay razón alguna válida, médica o económica, que no nos permita disponer en Puerto Rico de estos adelantos tecnológicos en la medicina moderna.

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# SOCIOS NUEVOS



## ACTIVOS

**Campos Vélez, Otto MD** - Escuela de Medicina de la Universidad de Guayaquil, Ecuador, 1964. Oftalmología. Ejerce en San Juan.

**Colón Crescioni, José Francisco MD** - New Jersey Medical School, 1978. Medicina General. Ejerce en Newark, NJ.

**Rosado Pacheco, Pedro A. MD** - Georgetown University, Medical School, Washington, DC, 1964. Pediatría. Ejerce en Ponce.

**Ortiz McWilliams, Julio A MD** - Georgetown University, Medical School, Washington, DC, 1982. Otorrinolaringología. Ejerce en Humacao.

**Torres Hernández, Delia MD** - Escuela de Medicina de la Universidad Central del Este, República Dominicana, 1972. Patología. Ejerce Humacao.

**Valentín González, Wilmer MD** - Escuela de Medicina de la Universidad Central del Este, República Dominicana, 1977. Cirugía. Ejerce en Bayamón.

## ACTIVO ESPECIAL

**Muñiz Camacho, Armando J MD** - Escuela de Medicina de la Universidad Autónoma de Santo Domingo, República Dominicana, 1987. Medicina General. Ejerce en Río Piedras.

## ACTIVO NO RESIDENTE

**Rivera Morales, Roberto MD** - Escuela de Medicina de la Universidad de Puerto Rico, 1977. Radiología. Ejerce en Florida.

## INTERNO RESIDENTE

**Velázquez González, Marcos A MD** - Escuela de Medicina Universidad Católica Madre y Maestra, República Dominicana, 1983. Medicina Interna.

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**Action:** Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it, however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

**Indications:** Yocon<sup>®</sup> is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

**Contraindications:** Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

**Warning:** Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

**Adverse Reactions:** Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.<sup>1,2</sup> Also dizziness, headache, skin flushing reported when used orally.<sup>1,3</sup>

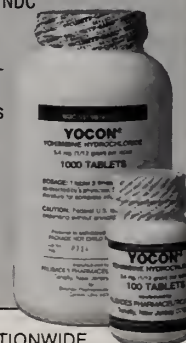
**Dosage and Administration:** Experimental dosage reported in treatment of erectile impotence.<sup>1,3,4</sup> 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.<sup>3</sup>

**How Supplied:** Oral tablets of Yocon<sup>®</sup> 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

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## AMERICAN ACADEMY OF PEDIATRICS

WHERE WE STAND: ISSUES FOR A HEALTHIER FUTURE FOR CHILDREN

### RECENT DEVELOPMENTS

**AIDS** - The AAP recommends that most children infected with the AIDS virus should be allowed to attend school and day care in an unrestricted manner, with the approval of their physician. Instances that may require a more restricted school environment are cases in which a student lacks control of his body secretions, has an open skin sore that cannot be covered or displays behavior such as biting. Mandatory screening of all children for AIDS should not be undertaken. The AAP also says the nation's schools should immediately initiate AIDS education programs in Kindergarten through twelfth grade, with candid emphasis in later grades.

**Circumcision** - The Academy says that circumcision has potential medical benefits and advantages, as well as inherent disadvantages and risks. Therefore, the Academy recommends that the decision to circumcise is one best made by parents in consultation with their physician. Factors affecting the parents' decision include esthetics, religion, cultural attitudes, social pressures, and tradition. Physicians should explain and discuss the benefits and risks of circumcision with parents, and informed consent should be obtained before the procedure is performed.

**Contraceptive advertising** - The Academy supports and encourages responsible non-prescription contraceptive advertising on radio and television. "There is evidence that increased (sexual) knowledge leads to increased use of contraception and decreased consequences of pregnancy and infection in those teenagers who are sexually active," says the AAP's Committee on Adolescence. There is no evidence that this information leads to increased sexual activity.

**Corporal punishment** - The AAP is opposed to the use of corporal punishment in schools, although many states still have legislation allowing it. Alternative methods for teaching self-control and responsible behavior are recommended.

**Drug screening** - The Academy is opposed to the involuntary drug screening of the older, competent adolescent — parental permission for screening is not sufficient. Student athletes should not be singled out for involuntary screening for drugs of abuse. Except for health-related purposes, such testing should not be a condition for participation in sports or any school function.

**Handgun control** - The Academy strongly urges active support of handgun control legislation. Elimination of these guns from the environment of children and adolescents would effectively reduce the injuries and fatalities they cause, especially suicide among young people.

**Lead poisoning** - Lead remains a significant hazard to the health of American children. Exposure to lead causes serious impairments to children at relatively low levels of exposure — the effects of which are largely irreversible. Although ideally, all preschool children should be screened, the AAP asks for screening of high risk children, as well as a national program to screen for and remove lead hazards from housing and restoration of federal funds to rid the U.S. of lead hazards.

**Missing children** - The perceived epidemic of missing children may be much smaller than the public has been led to believe. In fact, fingerprinting and other child identification programs may scare children and unnecessarily raise parental anxiety. The AAP advocates educating parents and children in preventive safety techniques and urges pediatricians to learn to detect stressful family situations that may predispose children to running away or being abducted by a non-custodial parent.

**Music lyrics and videos** - Although the Academy "strongly opposes censorship," it asks that the music industry exercise good taste and self-restraint in what is produced, especially because some rock music lyrics communicate potentially harmful health messages.

**Neonatal anesthesia** - There is increasing evidence that neonatal cortical function is far greater than previously thought. The AAP believes that local or systemic pharmacologic agents now available permit relatively safe administration of anesthesia or analgesia to neonates undergoing surgery. These agents should be given according to the usual guidelines for high risk, potentially unstable patients.

**Religious exemptions** - The AAP says statutes that permit denial of medical care necessary to prevent death or serious impairment to children on the grounds of their

parents' religious beliefs should not exist. The AAP urges state legislatures and regulatory agencies to remove religious exemption clauses and treat all parents and caretakers of children equally by state and federal laws. When parental practices have potentially harmful consequences for the child, the AAP says state intervention may be warranted.

*School-based health clinics* - The AAP supports the selective implementation of school-based health clinics in areas where the health care needs of the school age population are not being met.

*Television* - Television advertising and programming can adversely affect learning and behavior of children and adolescents in a number of significant areas: promoting a proclivity to violence, increasing the prevalence of obesity, detracting from time spent reading or using other active learning skills, conveying unrealistic messages regarding drugs, alcohol and tobacco, and portraying misleading sex roles and unrealistic sexuality.

Toy-based TV programs and television-activated toys are opposed by the AAP because of their disturbing effects on children. Both exploit children as consumers. The AAP also supports legislative efforts to improve children's programming content and promote more constructive viewing.

## Legislation

*Uninsured Children* - The Academy strongly supports legislative efforts to provide universal health insurance that addresses the special needs of children and pregnant women. Furthermore, the AAP has developed its own proposal to provide universal access to care and is working with members of Congress to implement this plan. The number of children without health insurance has been rising steadily since 1980 with as many as 16 million children through age 21 without insurance today. Ensuring universal access to health care for the growing population of uninsured children and pregnant women is the Academy's top priority and legislative goal.

*Child care* - The AAP supports federal child care legislation with strong provisions for health and safety standards. Pediatricians urge legislators to recognize that child care must be safe for children as well as affordable for parents. Inadequate licensing procedures and haphazard enforcement allow too many unhealthful and even life-threatening child care facilities to operate.

*Family Leave* - The AAP endorses federal legislation to enable working parents the flexibility to care for their children in critical situations without risking their jobs or their health insurance. A parent's presence during crucial moments in a child's life including birth, adoption, and serious illness, has a proven beneficial effect that both strengthens the bond between parent and child and enables sick children to recover more quickly.

*Children and Guns* - As child safety advocates, the AAP demands that federal initiatives address the need for gun control and gun safety to protect the lives of children and adolescents. Nearly 8.7 million children and adolescents have access to handguns, a proximity resulting in a growing number of tragic deaths and injuries. One of every 25 admissions to American pediatric trauma centers is due to gunshot wounds.

## General

*Alcohol use and abuse* - Alcohol is the drug most often abused by the largest number of children and adolescents. The Academy supports a ban on alcohol advertising similar to that of cigarettes, or equal time for counter advertising. The legal drinking age should be uniformly set at 21 years.

*Auto safety* - Infants and young children should always ride in car safety seats, preferably in the back seat, as it is safest. An infant or child should never ride in parent's arms. All U.S. states require that children ride in safety seats. The AAP continues to recommend the use of seat and shoulder belts for older children in both front and back seats of the car.

*Choking* - The AAP recommends the Heimlich maneuver for treatment of a choking child, except in infants younger than one year old. For infants under one year, the AAP says that back blows and chest thrusts if needed are still the best treatment for choking to avoid injury to the abdominal organs.

*DTP vaccine* - The Academy believes that children should receive the DTP (diphtheria-tetanus-pertussis) vaccine at two, four and six months of age with booster doses at 18 months and prior to school entry. Children who contract pertussis (whooping cough) are ten times more vulnerable to permanent brain damage than from the vaccine. Although the development of a better pertussis vaccine is desired, the Academy recommends the continued use of the present vaccine in the meantime to ensure protection of the nation's children against this highly infectious disease.

*Hib vaccine* - The AAP recommends that all children receive the *Haemophilus influenzae* type b conjugate vaccine at 18 months of age. A special effort should be made to immunize those children at high risk of Hib disease.

*Measles vaccine* - The AAP's new policy advises that the first dose be given as a combined measles, mumps and rubella (MMR) vaccination at 15 months of age and the second, also as MMR, at entrance to middle school or junior high school. The new recommendations aim to increase immunization in unvaccinated preschool-age children in high risk areas and to prevent the spread of measles in school and colleges by giving all children routine second doses later in life.

*Seat belts on school buses* - The AAP recommends that seat belts should be installed on all newly-manufactured school buses, regardless of their size and the number of pupils transported. Seat backs should be elevated to 28 inches, four inches above the height now mandated by federal regulations. Bus driver training should be mandatory in all school districts.

*Smoking* - During pregnancy: many studies have now shown that if a woman smokes during pregnancy, the birth weight and growth during the first year of her child's life is reduced. The range of indisputable effects runs from depressed breathing movements during fetal life to cancer, respiratory disorders and heart disease in later years. The AAP's message is clear —don't smoke when pregnant.

Passive smoking: Children of parents who smoke have



more respiratory infections, bronchitis, pneumonia and reduced pulmonary function than children of nonsmokers. The AAP supports legislation that would prohibit smoking in public places frequented by children. The AAP also supports a complete ban on tobacco advertising, harsher warning labels on cigarette packages, and increasing the cigarette excise tax.

**Toy firearms** - Because children who play with toy firearms may inadvertently play with real weapons which they mistake for toys, and because of the high number of injuries caused by toy firearms, the AAP supports enactment of federal safety standards regulating their use.

**Youth suicide** - The AAP strongly supports federal and state funding of programs and research efforts that address youth suicide. Questions about suicidal thoughts should be asked and explored during medical exams throughout adolescence. Pediatricians can play a major role in the prevention of youth suicide by being aware of risk factors and other signs associated with youth suicide.

## NUTRITION

**Breast feeding** - The benefits of breast feeding are so numerous that pediatricians strongly encourage the practice. Human milk is nutritionally superior to formulas for the content of fats, cholesterol, protein and iron.

**Cholesterol testing** - Regular elective cholesterol testing is suggested for children older than 2 years of age who have a family history of hyperlipidemia or early heart attack (less than 50 years of age in men, less than 60 years of age in women). The Academy opposes universal cholesterol testing because of the lack of standardization of testing. In addition, a single blood cholesterol level in children may not reflect day-to-day and seasonal variations and could result in unnecessary dietary treatment of a large number of children.

**Diet** - The AAP's Committee on Nutrition contends that there is no compelling new evidence to make recommendations concerning modification of the diet during the first two decades of life, without first assessing effects on growth and development. Diets that avoid extremes are safe for children with no special vulnerability. Current trends toward a decreased consumption of saturated fats, cholesterol and salt and an increased intake of polyunsaturated fats should be followed with moderation.

**Formulas** - When breast feeding is unsuccessful, inappropriate or stopped early, infant formulas provide the best alternative for meeting nutritional needs of infants. Dietary fat should not be restricted in this age group. Whole cow's milk also may be used after six months if adequate supplementary iron-containing feedings are given. Supplemental foods are recommended beginning four to six months of age.

The Academy policy of opposing the marketing of infant formula directly to the public is derived from its strong support and advocacy for breastfeeding. Because of the complexity of nutritional requirements during infancy, a physician or other qualified health professional should be involved in the decision on infant feeding options.

**Vitamins** - Normal, healthy children receiving a normal diet do not need vitamin supplementation over and above the recommended dietary allowances.

## PHYSICAL ACTIVITY

**All-terrain vehicles (ATV's)** - The AAP encourages a recall of three-wheeled all-terrain vehicles (ATV's) currently in use, and a ban on future commercial sales. The AAP also recommends that no child under the age of 16 be permitted to operate an ATV, three or four-wheel.

**Boxing** - The AAP opposes boxing in any sports program for children and young adults. Amateur boxing is potentially harmful to youth; protective headgear may actually increase brain injuries.

**Sports and fitness** - Because American children do not perform well on fitness tests, the AAP urges schools to maintain, if not increase, physical education programs. Programs should emphasize aerobic and "lifetime" activities such as bicycling, swimming, tennis and running, and decrease time spent on football, basketball and baseball — traditional school sports which are not particularly fitness-enhancing. Also, the AAP does not support structured infant exercise programs.

**Steroids** - Steroid misuse among professional and amateur athletes is a "major problem", says the AAP Committee on Sports Medicine. It condemns the use of steroids because of their known toxic side effects, and because their use is "just another form of cheating."

**Swimming** - The AAP feels that there is little justification for infant swimming programs. It is unlikely that these infants can be made "water safe" — in fact, parents can develop a false sense of security if they think their infant can "swim" a few strokes. Organized group swimming should be reserved for children more than three years of age.



**Agency for Health Care Policy and Research**

### ELECTRONIC FETAL MONITORING DURING LABOR DOES NOT IMPROVE PERINATAL OUTCOMES FOR PREMATURE

Surveys suggest that electronic fetal monitoring (EFM) is used during labor and delivery to monitor the unborn baby's heart rate in about 75 percent of births in the United States. A number of studies failed to show that EFM reduces perinatal mortality or the incidence of neurologic developmental disorders. A recent study, supported in part by the Agency for Health Care Policy and Research (AHCPR), also did not show any improvements in perinatal outcomes among infants born prematurely who underwent EFM. However, it indicated that EFM was associated with about a threefold risk of cerebral palsy when compared with the conventional practice of auscultation, in which a nurse uses a stethos-

cope to check the unborn infant's heart rate every few minutes during labor and delivery.

The new study, reported by Kirkwood K. Shy, M.D., M.P.H., and his colleagues at the University of Washington and Grace Hospital in Vancouver, British Columbia, Canada, compared the early neurological development of 93 prematurely born infants whose heartbeats were monitored electronically with 96 premature infants who underwent a structured program of periodic auscultation during labor and delivery. The researchers followed 173 of these infants to 18 months of age and found that cerebral palsy had been diagnosed in 16 of 82, or 20 percent, of those infants who had received electronic fetal monitoring, as compared with 7 of 91, or 8 percent, of babies whose heart rates were checked by stethoscope.

In addition, the researchers showed that the development of cerebral palsy was correlated with the duration of abnormal heart rates before delivery. The heart rate of a normal fetus may slow during uterine contractions. Very slow heart rates or failure of the heart rate to rise promptly to the normal range following a contraction may signal a potentially dangerous lack of oxygen. In this study, the average time that elapsed between detection of an abnormal heart rate and delivery was longer in the electronically monitored group (104.5 minutes) than in the group monitored manually by stethoscope (60.5 minutes). Dr. Shy and his colleagues suggest that the physicians who used EFM may have delayed the decision to perform a cesarean section either because they were falsely reassured by the technology itself, or because they did not believe the results were reliable.

Although the American College of Obstetricians and Gynecologists previously recommended electronic fetal monitoring for all high-risk patients, they issued a statement last year that auscultation is equally acceptable. In some hospitals, however, the shortage of nurses has made frequent checks of the fetal heart rate nearly impossible. For this reason, electronic fetal monitoring is likely to continue, since it is preferable to not checking the body's heart rate at all.

This research was supported under AHCPR grants HT00003 and HS04848. Details are in "Effects of Electronic Fetal-Heart-Rate Monitoring, as Compared with Periodic Auscultation, on the Neurologic Development of Premature Infants," by Kirkwood K. Shy, M.D., M.P.H., David A. Luthy, M.D., Forrest C. Bennett, M.D., Michael Whitfield, M.D., and others. The article appeared in the March 1, 1990, issue of *The New England Journal of Medicine*, 322(9), pp. 588-593.

#### NONCLINICAL INFLUENCES AND POLICY STRATEGIES ASSESSED FOR CESAREAN SECTION RATES

Nearly a quarter of all birth in the United States occur by cesarean section, making the operation one of the Nation's most common surgical procedures. This high utilization rate, coupled with the fivefold increase in the procedure since 1970, has prompted closer scrutiny by

insurers, health care providers, and patients.

Through examination of hospital data for 1986, a study funded by the Agency for Health Care Policy and Research (AHCPR) showed that cesarean section rates in California varied widely by payment source. Women with private health insurance had the highest rate of cesarean section (29 percent) of all groups of patients in the study. Lower rates were found for women covered by health maintenance organizations (HMOs) and for women covered by Medi-Cal, the California Medicaid program. Women covered by Kaiser-Permanente, a large hospital-based HMO, had almost the same cesarean section rate (20 percent) as women who were self payers (19 percent). The lowest cesarean section rates were for women covered by California's Indigent Services program. Women in this last category had a cesarean section rate of nearly 16 percent—just over the rate of privately insured women.

Results also showed that a previous cesarean section was the most common indication for the procedure. Repeat cesarean sections accounted for slightly more than a third of all cesarean births examined in the study. Repeat cesarean section rates ranged from 92 percent for privately insured women, to 80 percent for Kaiser-Permanente patients, to 75 percent for women covered by the Indigent Services program.

According to principal investigator Randall Stafford, Ph.D., of the University of California at Berkeley, study findings suggest that several factors contributed to the observed differences in cesarean section rates among payers. These include direct and indirect financial incentives as well as an emphasis on peer review. Kaiser-Permanente, whose cesarean section rate was nearly 10 percent lower than that of private insurers, stresses peer review. In the case of Medi-Cal, reduced physician and hospital reimbursement may have helped temper the inclination to perform the procedure. The desire of self-pay women to avoid the higher cost of cesarean section may discourage use of the procedure. In addition, these women tend to deliver in public hospital, where additional institutional constraints may reduce the number of procedures.

According to Dr. Stafford, if private insurers, smaller HMOs, and Medi-Cal had the same cesarean section rates as Kaiser-Permanente, as a group they would have performed 22,500 fewer procedures in 1986 and thereby saved an estimated \$51 million.

The analysis, which was conducted under AHCPR grant HS06116, was based on 112,730 cesarean sections performed in California hospitals in 1986. Details are in "Cesarean Section Use and Source of Payment: An Analysis of California Hospital Discharge Abstracts," by Dr. Stafford, which was published in the March 1990 issue of the *American Journal of Public Health* 80(3), pp. 313-315.

In a separate study, Dr. Stafford reviewed the literature on policy strategies to control the rise in cesarean section rates. Formal hospital-initiated programs using locally implemented clinical guidelines and peer review showed the greatest promise, reducing cesarean section rate by 20 percent. Consensus development conferences and continuing medical education do not appear succes-



sful. Alternative strategies—including external review of obstetric practices, public dissemination of cesarean of cesarean section rates, and charges in physician and hospital reimbursement—are being tried by some organizations, but the effectiveness of these efforts in controlling cesarean section rates has not yet been evaluated. The literature suggests that effective control of the use of cesarean section may require a combination of educational and financial strategies coupled with consumer participation.

The literature review is described in “Alternative Strategies for Controlling Rising Cesarean Section Rates,” By Dr. Stafford. The article was published in the February 2, 1990, issue of the *Journal of the American Medical Association* 263(5), pp. 683-687.

### COMPUTERIZED ANTIBIOTIC THERAPY MONITORING APPEARS PROMISING

Computer-assisted monitoring appears to be an efficient and promising method for identifying and correcting errors in antimicrobial prescribing, according to a new study funded by the Agency for Health Care Policy and Research (AHCPR). The conclusion by researchers led by Reed M. Gardner, Ph.D., of the LDS Hospital in Salt Lake City, Utah, is based on a study of 1,632 hospitalized patients whose microbiology specimens were tested for susceptibility (sensitivity and resistance) to antibiotic. The results were then fed into a hospital information system known as HELP (Health Evaluation through Logical Processing) that integrates data from various departments in the hospital. The HELP system includes interactive programs that screen for inconsistencies between patients' antibiotic therapy and test results. When mismatches are found, the computer generates an alert. The hospital's clinical pharmacists then notify the prescribing physician who makes the ultimate decision as to whether the alert is true and if so, how to respond.

During the study, 696 alerts were produced of which 420 were judged to be true by the prescribing physicians. Overall, antibiotic therapy was changed or started in 30 percent of accepted alerts. Although physicians claimed not to have changed antibiotic therapy for the remaining 70 percent of the true alerts because their patients were improving clinically, medical records show they switched antibiotics in 34 instances within 24 hours of receiving a warning. Nearly 355 of the true alerts involved patients who were already receiving antibiotic. For patients not receiving antibiotics, drug therapy was started 73 percent of the time. The investigators also examined the speed with which physicians received the alerts. Almost half the alerts reached physicians before they got the results of antibiotic susceptibility tests which were sent through normal channels.

The study was funded under AHCPR grant HS05319. Details are in “Therapeutic Antibiotic Monitoring: Surveillance Using a Computerized Expert System,” by Stanley L. Pestotnik, R.Ph.; R. Scott Evans, Ph.D.; John P. Burke, M.D.; Reed M. Gardner, Ph.D.; and David C. Classen, M.D. The article was published in the

January 1990 issue of *The American Journal of Medicine* 88, pp. 43-48

### CURRENT STATUS OF AUTOMATED EXTERNAL DEFIBRILLATORS REVIEWED

The automated external defibrillator (AED), a new technology for emergency care, has made it possible for minimally trained emergency personnel, community responders, and family members of high-risk persons to deliver on-the-spot, early defibrillation to patients in cardiac arrest. This is critical because immediate electrical countershock is the most effective treatment available for ventricular fibrillation, a lethal cardiac arrhythmia. Approximately 85 percent of cardiac arrest patients are in ventricular fibrillation for several minutes following collapse. For each minute that elapses, there is a decline of 7 to 10 percent in the probability that the patient will survive, with or without defibrillation. If defibrillation is delayed longer than 10 to 12 minutes, there is almost no chance of survival.

AED technology has been widely adopted for use by emergency responders and has reached the stage of accepted practice, or even standard of care. Adoption of the technology has been proposed for three clinical areas because it could lead to reduced mortality—prehospital care, community emergency care, and home care for high-risk patients. In prehospital care, AEDs are operated by emergency medical technicians (EMTs)—emergency medical workers usually trained in basic life-saving skills including cardiopulmonary resuscitation—or other first responders, such as firefighters. Community emergency care involves using lay responders, such as security guards and recreation or health club managers, to operate AEDs. In home care, family members or companions of persons at high risk of heart attack are trained to operate the device.

Several studies have found improvements in survival rates when EMTs have used AEDs; with other users, however, AED use has been less positive. In a logical extension of the early defibrillation principle, AEDs have been placed in community settings where, as mentioned above, they have been operated by minimally trained community responders, such as building guards, recreation center managers, and restaurant workers. While this concept appears to be sound and the AEDs have been used successfully in a number of instances, there have been several serious problems. These problems include failure by community responders to recognize cardiac arrest, forgetting to retrieve AEDs from where they are kept, improperly attaching the device to victims, and improper operation.

The most discouraging results have involved use of AEDs in the home by family members of high-risk patients. Studies of such use have recorded some successes, but there have also been numerous unanticipated problems, including unwillingness of patients or their physicians to participate and failure of family members to retain skill levels, as well as the improper use of AEDs.



## EXERCISE REDUCES BLOOD PRESSURE AND LDL LEVELS

More reasons to exercise —it may eliminate the need for drugs to reduce mild hypertension while it lowers “bad” cholesterol and raises “good” cholesterol a report in the *Journal of the American Medical Association* finds.

Another finding: certain weight training programs do not adversely affect the blood pressures of hypertensive patients, according to Michael H. Kelemen, MD, of the Department of Medicine, The Columbia Medical Plan, Columbia, Md., and his colleagues.

Investigators set out to see if adding antihypertensive drugs to a weekly workout routine would add to any decrease of blood pressure and/or LDL cholesterol levels.

Overall, the answer was no, the drugs didn’t provide added benefits to the antihypertensive effects of exercise, the authors conclude.

“We conclude that patients engaged in a regular program of exercise may not need drug therapy for control of mild hypertension,” the authors write. “We (also) conclude that an exercise training program that includes circuit weight training appears to be safe in patients with mild hypertension.”

Two antihypertensive drugs, diltiazem and propranolol, were used in the study of 52 sedentary men (47 white, five black), along with a placebo. The participants had a history of hypertension, but did not show any signs of coronary, valvular heart, kidney, neurological disorders or any history of alcohol or drug abuse.

The exercise program lasted 10 weeks, with the men working out three times each week. Each session consisted of 30 minutes of weight training, followed by a 20-minute aerobic workout of walking, jogging or riding a stationary bicycle.

Researchers found the men’s systolic and diastolic blood pressure dropped after the 10-week exercise training program ended. And while there was a trend toward a more immediate blood pressure control in the participants using either of the antihypertensive drugs, there were no differences in blood pressure reduction

between the three groups after a month of exercise.

The latest study confirms earlier findings that exercise even without drug therapy decreases total cholesterol and LDL cholesterol levels. The authors also found the exercise raised the levels of HDL cholesterol.

In those men taking the antihypertensive drugs, those in the propranolol group recorded lower HDL levels, whereas those in the diltiazem and placebo groups did not show any drop in HDL levels, the study found.

In this study, the men ate what they wanted. There were no specific dietary restrictions.

The weight training program did not push the men to their limits; clinical acceptable blood pressure levels were detected when lifted was limited to 40 percent of maximum effort, the study found.

*JAMA May 23, 1990*

## REPORT: DON'T START CYSTIC FIBROSIS TESTS

Despite the technological ability and commercial pressures to do so, mass screenings for cystic fibrosis should not begin anytime soon, according to a report in the *Journal of the American Medical Association*.

The clerical and lab errors, patient confusion and societal stigmatization that marred earlier mass screening efforts may be magnified with the proposed CF tests, according to Benjamin S. Wilfond, MD, and Norman Fost, MD, MPH, of the Department of Pediatrics and the Program in Medical Ethics, University of Wisconsin, Madison.

“The potential for CF carrier screening programs will create an entrepreneurial opportunity that will dwarf all previous screening programs,” the authors write.

Malpractice fears also may accelerate the momentum toward CF testing.

“Obstetricians could be persuaded to offer carrier screening because of a concern for potential liability for “wrongful birth” if screening were not offered and a child were subsequently born with CF,” the authors warn.

Cystic fibrosis is an inherited disease, and its victims suffer chronic lung infections and an inability to absorb fats and other food nutrients. The CF defect is of the recessive type, meaning a person must inherit the gene from each parent. People who inherit a gene from just one parent are known as carriers. It is the most common potentially lethal gene in white Americans—estimated to be present in one out of every 2,500 live birth of U.S. whites. In nonwhites, the gene is very rare. In the U.S., more than 8 million people carry the CF gene without knowing it.

The current 75 percent detection rate carries a mixed blessing, according to the authors.



People who test negatively reduce the risk they are carriers from one in 25.5 to one in 99. The chances a couple from the general population would be reduced from one in 2,500 to one in 10,100 if one partner tested negative and one in 39,200 if both partners tested positively.

Conversely, misinformation about results —be they accurate or inaccurate— can be troublesome, the report says.

"Such errors can cause significant harm when clients based reproductive decisions on erroneous or poorly understood information," their report says. "The normal problems of genetic counseling will be compounded due to the unusual complexity of the test at the present time."

The authors predict the price tag for such a mass screening program could total \$2.2 million for each cystic fibrosis birth avoided. They also say the Cystic Fibrosis Foundation opposes a screening plan until its safety and efficacy can be substantiated.

The report recounted problems faced by those screened in the early 1970s for sickle cell anemia and how the confusion in New York between the disease and the carrier state led to insurance companies denying coverage to sickle cell carriers.

Societal discrimination could be worse if CF screenings became commonplace.

"Even though it might be claimed that the primary goal is to inform people that they should consider the possibility of screening, a social consensus could emerge that would be more directive in discouraging carriers from bearing affected children," the report says.

Pilot studies should continue to learn more about laboratory errors and the educational and counseling aspects of CF testing, the authors conclude.

*JAMA May 22, 1990*

#### **MEDICAL CENTER RESEARCH AND PRIVATE INDUSTRY: INTERESTS IN CONFLICT?**

Increases in private funding levels mean medical centers and their biomedical researchers need to be aware of potential conflicts of interest, according to a report in the *Journal of the American Medical Association*.

"Although these types of arrangements are relatively new, they are fast becoming important to the survival of both industry and academia as the research environment becomes increasingly competitive," says the joint report from the AMA's Scientific Affairs and Ethical and Judicial Affairs Councils.

They report that nearly half of all biotech firms support research in universities; 90 out of the top 100 universities conducting biotech research receive industry money; and nearly half of all faculty researchers in biotechnology are employed as industry consultants.

The most frequent type of medical center-industry relationship essentially is a fee-for-service arrangement in which a company pays a clinical investigator to carry out a research protocol, the report says.

A second arrangement arises when a researcher submits an unsolicited proposal directly to a commercial

company. Providing the basic rules of scientific propriety are followed, both relationships are appropriate, the report says.

"Problems may arise when the clinical investigator and/or medical center has a direct financial interest in the research program," the report states. "This is especially true in situations in which drugs, devices, or other similar products are being examined...Economic incentives may introduce subtle biases into the way research is conducted, analyzed, or reported, and these biases can escape detection by even careful peer review."

The report recommends ethical guidelines for such relationships based on two principles: "First, the researcher may ethically share in the economic rewards of his or her efforts...However, the researchers may not reap profits that are not commensurate with the value of his or her actual efforts." Applications of the principles would, for instance, ethically prohibit a researchers from using inside information to buy or sell a company's stock.

Even in the event of ethical economic relationships, the report recommends full disclosure to "assuage public (and professional) doubts about the propriety of a research arrangement." Such disclosures should be made to the medical center, funding organizations and journals that publish the results.

"Medical centers should be urged to develop these policies and also to provide clinical researchers with guidance on the implementation of complex research relationships," the report says.

*JAMA May 23, 1990*

#### **HEART DISEASE RISK FACTORS FOUND IN PREDIABETIC PATIENTS: STUDY**

Individuals who eventually become diabetic show a variety of cardiovascular risk factors before they show clinical signs of diabetes, a study in the *Journal of the American Medical Association* concludes.

These risk factors may be present for many years before the onset of diabetes, and may contribute to major vascular disease and diabetic complications, say the authors, Steven M. Haffner, MD, MPH, of the Division of Clinical Epidemiology, The University of Texas Health Science Center, San Antonio, and colleagues.

Their findings lend support to the theory that the "prediabetic phase" could be a period of increased cardiovascular risk. "Unlike microvascular complications, where 'the clock starts ticking' with the onset of clinical diabetes (ie, hyperglycemia), in the case of macrovascular disease, the clock may start ticking decades earlier," they write.

The researchers studied the cardiovascular risk factors of 614 initially nondiabetic Mexican Americans to determine how many persons would subsequently develop type II (non-insulin-dependent) diabetes. The following measurements of clinical status were obtained: total, high- and low-density lipoprotein cholesterol levels, triglyceride, fasting glucose and insulin levels, plasma glucose levels two hours after ingestion of

glucose, body mass index (BMI), and blood pressure. The patients were reexamined eight years later as part of the San Antonio Heart Study, a large study of diabetes and cardiovascular disease.

Forty-three patients became diabetic after their baseline examination; 571 remained nondiabetic. Those who developed diabetes had higher levels of total and low-density lipoprotein ("bad") cholesterol, triglyceride, fasting glucose and insulin, two-hour glucose, BMI, and blood pressure prior to disease onset than patients who did not develop diabetes. They also had lower levels of high-density lipoprotein ("good") cholesterol than their nondiabetic counterparts. Most of the differences remained after the researchers made several adjustments. These results were seen even in patients whose glucose tolerance at baseline was normal, not just those whose baseline glucose tolerance was impaired.

"The present data show that prediabetic subjects are characterized not only by hyperinsulinemia, but also by a more atherogenic pattern of cardiovascular risk factors compared with subjects who do not convert to diabetes," the authors say.

"Our results suggest that to reduce the cardiovascular risk of diabetic individuals to that of nondiabetic individuals, it may be necessary to intervene before the onset of clinical diabetes, since the 'clock has already begun to tick,' " they conclude.

"Coexisting risk factors are especially relevant in type II, non-insulin-dependent diabetes, because this disease confers the most risk for accelerated atherosclerosis and the risk is most difficult to correlate specifically with glycemia," writes Christopher D. Saudek, MD, of the Department of Endocrinology, The Johns Hopkins Hospital, Baltimore, Md., in an accompanying editorial.

But since non-insulin-dependent diabetes develops gradually, "any assessment of duration of type II diabetes is suspect," he says. A complex network of factors is probably responsible for the onset of the disease. In the rush to treatment, physicians may be "overinsulinizing" diabetic patients. "It may be better to attack the insulin resistance itself, most directly by reducing obesity," the author says.

"Early assessment of risk-factor status and aggressive attention to, particularly, weight reduction could move many people off a very dangerous path" toward diabetes, Saudek concludes.

*JAMA June 6, 1990*

### DRAMATIC RESULTS WHEN THE VERY OLD "PUMP IT UP"

It's never too late. Start a group of frail 90-year-old on a regimen of high-intensity weight training and they'll respond with big jumps in muscle strength, size and mobility, a study in the *Journal of the American Medical Association* concludes.

"Remarkable" improvements resulted from an eight-week weight-training program completed by a group of sedentary, institutionalized men and women, write Maria A. Fiatarone, MD, of the U.S. Department of

Agriculture Human Nutrition Research Center on Aging at Tufts University, Boston, Mass., and her colleagues.

"The major finding for this study is that a high-intensity weight-training program is capable of inducing dramatic increases in muscle strength in frail men and women up to 96 years of age," the authors write. "However, just as in younger individuals, these changes in muscle function are not maintained in the absence of continued training."

This weight-training program focused on leg muscles, specifically the quadriceps. Three times a week, 10 subjects from the Hebrew Rehabilitation Center for Aged in Boston performed three sets of eight repetitions with each leg on a weight-lifting machine. As the study progressed, the elderly weight lifters raised and lowered increasing amounts of weights.

The very old weight lifters were not in tip-top shape when they began.

Seven of the 10 participants had arthritis, six had coronary heart disease and four had hypertension, the study notes. Nine out of ten completed the program. One man, who previously had a hernia repaired, dropped out prematurely at the suggestion of the researchers.

The 90 percent who successfully finished the program reported a few aches and pains in their hips and knees, the authors write, but none needed any analgesic pain relief. No cardiovascular or blood pressure complications were detected.

The final results were impressive.

Both men and women reported an average strength gain after eight weeks of 174 percent (plus or minus 31 percent) in their right legs, the study says. The absolute weight lifted increased from approximately 16 pounds to approximately 43 pounds in the right leg and from approximately 15 pounds to 41 pounds in the left leg.

"Strength gain was progressive throughout the protocol and had not plateaued at eight weeks," the authors write. "Responsiveness to training was not different in men vs women."

The increase in lower extremity strength ranged from 61 percent to 374 percent since the study began, with participants showing an average three- to four-fold increase in strength over the eight-week course, the study shows.

"The favorable response to strength training in our subjects is remarkable in light of their very advanced age, extremely sedentary habits, multiple chronic diseases and functional disabilities, and nutritional inadequacies," the authors conclude.

*JAMA June 13, 1990*

### INTERVENTION HELPS LOW-BIRTH-WEIGHT BABIES

Ten years of technological advances have markedly improved the survival rate of low-birth-weight (LBW) infants, only to see these babies run a greater risk than normal-weight infants for medical complications and developmental delay.

A new study published in the *Journal of the American Medical Association* concludes that early and comprehen-



sive intervention can significantly improve IQ scores and other development measures for LBW children.

Organized by the Infant Health and Development Program, Stanford, California., the study is the largest reported multisite randomized clinical trial to evaluate the effects of child development and family support services combined with regular follow-up with a pediatrician on LBW infants.

The study was conducted at eight sites around the country, including Dallas, Texas; New Haven, Conn.; Seattle, Wash.; and Little Rock, Ark. Nearly 1,000 infants were studied for 36 months, from birth to age three years.

"The results of this study indicate the effectiveness of a comprehensive intervention, even for biologically vulnerable infants," the authors write. "Our findings show that the children who received the intervention experienced: significantly higher IQ scores; significantly fewer maternally reported behavior problems; and a small, but significant, increase in maternally reported morbidity (illness), with no evidence of an increase in reported serious health problems."

The infants at the eight sites were divided into two birth-weight groups: infants who weighed 2000 grams (about 4.3 pounds) or less and infants who weighed 2001 grams to 2500 grams (about 5.5 pounds). The birth-weight groups were randomly subdivided; one-third received intervention, while the remaining two-thirds received only traditional pediatric follow-up.

Intervention began with weekly home visits for the first year, changing to bi-weekly visits thereafter. The visitor provided family support, health and developmental information, and implemented two curricula—one emphasizing the cognitive, linguistic and social development of the child, and the other teaching parents to manage self-identified problems.

After the first year the intervention children began attending a child development center five days a week. Center staff continued the learning curriculum implemented by the home visitors. Also at one year, parents began attending bimonthly group meetings which provided information on child rearing, health, and safety, as well as some social support.

Regular assessment were done on all the children.

"At corrected age 36 months, the intervention group had significantly higher mean IQ scores than the follow-up group," the authors write. The behavior weight intervention group averaged 13.2 points higher and the lower weight group averaged 6.6 points higher than the follow-up group. "The adjusted odds for having IQ scores less than 70, i.e., the mental retardation range, were 2.7 times greater in the follow-up group," they report.

On a child behavior checklist, follow-up children were 1.8 times more likely than intervention children to have a score which "correlated with clinically evident behavior problems." For health status, there was an increase in maternally-reported minor illness in the lower weight intervention group, but no differences in serious health conditions.

"We conclude that this comprehensive and intensive early intervention program shows substantive promise of decreasing the number of LBW premature infants at risk

for later developmental disability," the authors write.

In an accompanying editorial, Julius Richmond, MD, of the Division of Health Policy Research and Education, Harvard University, Boston, Mass., writes, "The implications of this findings for public policy are considerable at a time when day care and early intervention programs are expanding. Any efforts to enhance the cognitive and behavioral development of these children who are at greater developmental risk because of low birth weight are potentially important for their functioning in school.

"At a time when the costs of programs receive much attention, it is important to emphasize that comprehensive intervention programs for low-birth-weight infants need not be financially prohibitive... We should recognize the potential for long-term saving through the prevention of disabilities and their consequent costs."

*JAMA June 13, 1990*

### MICROSCOPIC CHANGES SEEN IN SKIN TREATED WITH RETIN-A

There is now more evidence tretinoin (Retin-A) helps improve the appearance of skin damaged by sun exposure, according to a study in the *Journal of the American Medical Association*.

Photoaged skin samples treated with Retin-A show a significant increase in the number of collagen bundles called "anchoring fibrils" found in underlying skin layers, say David T. Woodley, MD, of the Department of Dermatology, Stanford University Medical Center, Stanford, Calif., and colleagues. Increasing these skin components may straighten fine wrinkles and contribute to the overall clinical appearance of photodamaged skin, the authors believe.

Prior to administering tretinoin, skin biopsies were taken from each forearm of six white women (age range, 36 to 55). Using an electron microscope, the number of anchoring fibrils—delicate bundles of collagen which "anchor" the outside layer of skin onto the inner connective tissue—were defined and counted. The women then applied tretinoin (0.1 percent) cream to the skin of one forearm and placebo to the other each day for four months. At the end of the study, biopsies were again taken and the number of anchoring fibrils counted.

After four months, skin treated with tretinoin showed double the number of anchoring fibrils compared to skin treated with placebo. Although the number of patients in the study was small, the results are statistically significant, the authors report.

Skin cells produce the substance known as collagenase in response to ultraviolet (UV) light. Tretinoin has been shown to effectively slow the production of collagenase.

"It is possible there is a connection between UV light exposure, accelerated collagenase production, and degradation of anchoring fibril collagen," the authors write. They theorize that when photoaged skin is treated with the collagenase inhibiting Retin-A, skin structures may be repaired, leading to improvement in the skin's appearance.

*JAMA June 13, 1990*

## LIVING IN A NOISY WORLD: HEARING LOSS AFFECTS MILLIONS

Noisy surroundings, beginning even before a newborn leaves the hospital, cause hearing loss for millions of Americans, according to a report in the *Journal of the American Medical Association*.

More than one in every 10 Americans suffer varying degrees of hearing loss, that can be "insidious permanent and irreparable, causing communications interference that can substantially affect the quality of life," write the authors from the National Institutes of Health Consensus Development Conference on Noise and Hearing Loss.

"More than 20 million Americans are exposed on a regular basis to hazardous noise levels that could result in hearing loss," the report concludes. "Longer exposure to less intense but still hazardous sounds, commonly encountered in the workplace or in certain leisure-time activities, exacts a gradual toll on hearing sensitivity, initially, without the victim's awareness."

It was also concluded that "inconsistent compliance and spotty enforcement" of existing laws and regulations continue to result in noise-induced hearing loss (NIHL).

Nearly anyone could fall victim to this type of preventable hearing loss. Musicians, firefighters, police officers, construction and factory workers, and truck drivers constantly face deafening noise levels. But they're not alone.

"Live or recorded high-volume music, recreational vehicles, airplanes, lawn-care equipment, woodworking tools, some household appliances, and chain saws are examples of nonoccupational sources of potentially hazardous noise," the conference experts concluded. "Unfortunately, although NIHL is preventable, our increasingly noisy environment places more and more people at risk."

The effect of repeated noise that is too loud is cumulative and currently is not treatable, the report says.

"It does not matter if the sound is generated by a machine in the workplace, by an amplifier speaker at a rock concert, or by a snowmobile," the report says. "The acoustic energy of the sound, (or decibel) not its source, is important." An typical conversation between two people occurs between 65 and 70 decibels. Sounds louder than 85 decibels are potentially dangerous, the conference concludes.

Even premature infants exposed to the noisy environment of a neonatal intensive care unit may be at risk of hearing loss, the report says.

The conference panelists urged that newborn nurseries, including neonatal intensive care units, be made quieter, and "affordable, effective hearing protectors" should be available to the public.

"Governmental regulations that currently apply to most noisy industries should be revised to encompass all industries, strengthened in certain requirements, and strictly enforced, with more inspections and more severe penalties for violations," the conference members write.

## CHLAMYDIA, DOUCHING LINKED TO ECTOPIC PREGNANCY

Women who were infected with the sexually transmitted organism *Chlamydia trachomatis* may suffer more than twice as a high a risk for a pregnancy that develops outside the womb—ectopic pregnancy (EP)—according to a study in the *Journal of the American Medical Association*.

"The United States is currently experiencing an epidemic of ectopic pregnancy," write Joan M. Chow, MPH, DPH, of the School of Public Health, University of California, Los Angeles, and colleagues.

"Ectopic pregnancies account for 11 percent of maternal mortality, reduces subsequent fertility, and increases chances of subsequent EPs," the authors write. A reported a fourfold increase in ectopic pregnancies occurred from 1970 to 1985 (78,400 EPs reported in 1985); the cost associated with EPs in 1985 was estimated to be \$462 million.

The study compared at 306 women who had ectopic pregnancies and 266 women who had more normal uterine pregnancies carried to term. Almost 70 percent of the ectopic patients were relatively poor, white Hispanic women.

"Our data suggest that past chlamydial infection is associated with a greater than twofold increased risk of EP," the authors write, adding, "We found that history of douching and current douching remain associated with EP."

"There is a strong need to identify the most effective means of reducing EP rates," they write. "This study has found prior chlamydial infection and current douching to be highly prevalent, independent factors with strong associations with EP. Both factors are potential targets for intervention and modification."

In an accompanying editorial, Bruce B. Dan, MD, senior contributing editor for *JAMA* disagrees with the concluding remarks of the authors who say changing douching behavior could have more impact in reducing ectopic pregnancy. "Rather than suggest changes in douching regimens, physicians would do better by telling women at every opportunity how to protect themselves from acquiring chlamydial infections," Dan writes. "This strategy would also serve to decrease the incidence of gonorrhea, syphilis, human immunodeficiency virus infection, and hepatitis B infection, something a change in douching practices is unlikely to do."

*JAMA* June 20, 1990





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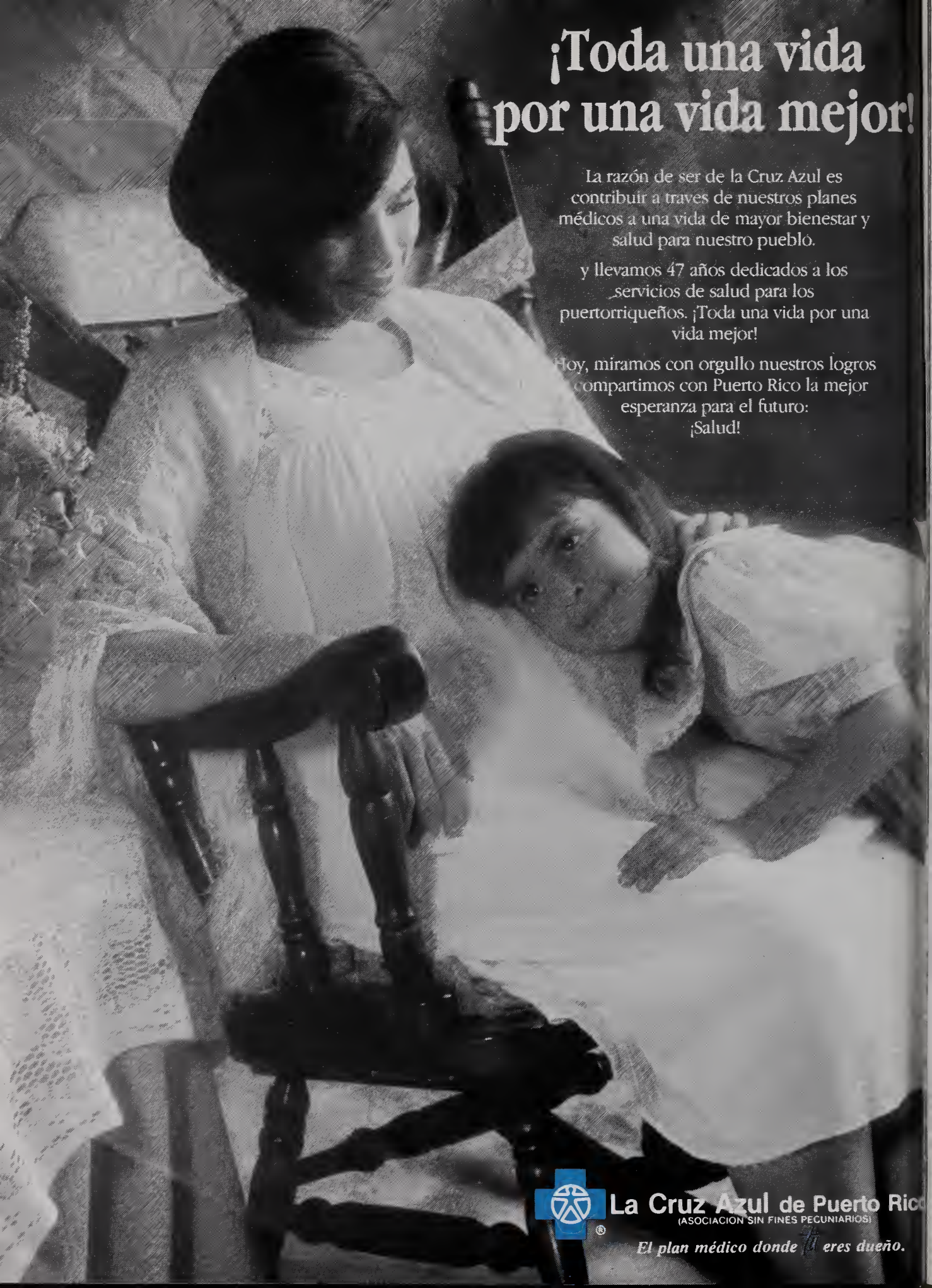
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VOL.82 / NUM.8

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**"YES, THERE IS  
LIFE AFTER  
BREAST CANCER.  
AND THAT'S THE  
WHOLE POINT."**

**—Ann Jillian**



A lot of women are so afraid of breast cancer they don't want to hear about it.

And that's what frightens me.

Because those women won't practice breast self-examination regularly.

Those women, particularly those over 35, won't ask their doctor about a mammogram.

Yet that's what's required for breast cancer to be detected early. When the cure rate is 90%. And when there's a good chance it won't involve the loss of a breast.

But no matter what it involves, take it from someone who's been through it all.

Life is just too wonderful to give up on. And, as I found out, you don't have to give up on any of it. Not work, not play, not even romance.

Oh, there is one thing, though.

You do have to give up being afraid to take care of yourself.



## *Nuestra Portada*

**Francia.** Obra del artista puertorriqueño Jorge Zeno. El autor nació en Washington, DC en 1956.

Desde pequeño comenzó a expresar sus inquietudes artísticas en cuadernos de dibujo, prosiguiendo sus estudios de gráfica en la Escuela de Artes Plásticas de Puerto Rico con el Maestro José Alicea en 1975.

Ya en 1978 gana el premio en un Certamen de Arte de la H.F.C. en Chicago, logrando además, mención honorífica con el grabado "Empecé a soñar."

Las obras y lienzos más importantes de la producción inicial de Jorge Zeno nos anuncian la tónica de su futuro trabajo: Jorge Zeno es un pintor imaginativo, espontáneo, inquieto, moderno y de gran versatilidad.

Ha expuesto sus obras en algunas de las más importantes galerías profesionales de Puerto Rico y Nueva York. La que aparece en la portada fue exhibida en el museo de Luxemburgo en París y pertenece a una colección privada en Puerto Rico.

La Junta Editora agradece su colaboración al autor y al Dr. Manuel Pérez-González sus gestiones para poder reproducir la obra.



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# CLINICAL STUDIES

## Albinism and Hermansky-Pudlak Syndrome in Puerto Rico

Carl J. Witkop, DDS, MS<sup>1</sup>  
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Stanley X. Cal, MD<sup>7</sup>  
James G. White, MD<sup>2</sup>

**Abstract:** Five types of oculocutaneous albinism and two types of ocular albinism were found among 349 Puerto Rican albinos. The most prevalent type of albinism was the Hermansky-Pudlak syndrome (HPS). HPS was observed in five of every six albinos in Puerto Rico. The prevalence of HPS was highest in the northwestern quarter of the island, affecting approximately one in 1,800 persons, and approximately one in 22 are carriers of the gene.

HPS is an autosomal recessively inherited triad of a tyrosinase-positive type of albinism, a hemorrhagic diathesis due to storage pool deficient platelets and accumulation of ceroid in tissues. The pigmentary phenotype of HPS albinos resembled that of any other type of oculocutaneous or ocular albinism. The most reliable method of diagnosing HPS is by a deficiency of platelet dense bodies observed by electron microscopy.

The accumulation of ceroid in the tissues is associated with fibrotic restrictive lung disease and granulomatous enteropathic disease. The enteropathic disorder resembles Crohn's disease and with few exceptions, had its onset after 13 years of age. The major causes of death were fibrotic restrictive pulmonary disease, hemorrhagic episodes and sequelae of granulomatous enteropathic disease. Menometrorrhagia was common in women with HPS. No immune deficiency was found in HPS patients. The majority of patients with HPS had visual acuities of 20/200 or worse and consequently were legally blind. Albinos of all types, including HPS, lacked binocular vision due to nearly complete crossing of the optic tracts.

There are ten phenotypes of oculocutaneous albinism (OCA) and four types of ocular albinism (OA) that can be distinguished on the basis of their clinical features, the ability of epilated hairbulbs to form pigment when incubated in various substrates, the ultrastructure of melanosomes, and by matings of albinos whose offspring indicate complementation or allelism of the genes involved.<sup>1, 2</sup> One type, the Hermansky-Pudlak syndrome (HPS)<sup>3</sup> affects many Puerto Ricans<sup>4, 5</sup> and accounts for the high prevalence of albinism on the Island.

HPS is an autosomal, recessively inherited triad of tyrosinase-positive oculocutaneous albinism, a bleeding diathesis due to storage pool deficient platelets and a lysosomal ceroid storage disease. Restrictive lung disease and a granulomatous enteropathy resembling Crohn's disease occur frequently in HPS patients; renal failure may develop in older individuals.

We have carried out an epidemiologic study over a five year period from 1985-1989 to determine the prevalence of various types of albinism in Puerto Rico and to determine if the frequency of the HPS type of OCA is the major contributor to the high prevalence of albinism in Puerto Ricans. We have continued our basic and clinical investigations into the pathogenesis and morbid consequences of HPS which began in 1971. The present study will describe the results of the epidemiologic study and updates current information on HPS based on results of our recent investigations.

### Materials and Methods

#### Epidemiologic Study

Persons with albinism were ascertained among patients at the Rincon Rural Health Initiative Clinic, among the members of the National Organization of Albinism and Hypopigmentation (NOAH) and from students and alumni of the Loaiza Cordero Institute.

Department of Oral Sciences, School of Dentistry;<sup>1</sup> Department of Laboratory Medicine;<sup>2</sup> Department of Medicine;<sup>3</sup> Department of Ophthalmology;<sup>4</sup> School of Medicine, University of Minnesota, Minneapolis, MN; U.S. Public Health Service, San Juan, Puerto Rico;<sup>5</sup> Department of Medicine, University of California at Los Angeles, CA;<sup>6</sup> University of Texas Southwestern Medical School, Dallas, TX.<sup>7</sup>

Supported by NIH Grants GM P01-22167, HL-R01-11880, Clinical Research Center Program Grant PR 400 and March of Dimes 1-886.

Written informed consent was obtained from each participant. Only persons who met the criteria of albinism,<sup>1, 2, 5</sup> congenital hypopigmentation of skin, hair and eyes (or eyes only), nystagmus, hypoplasia of the fovea, diaphanous irides on transillumination and decreased visual acuity, were included in the study.

A kindred chart, a genetic and medical history, a brief physical examination, a blood sample, and where indicated, hairbulbs and punch skin biopsies for ultrastructure were obtained to make a diagnosis of the type of albinism. A 24-hour urine sample was obtained for quantitative analysis of dolichols and for microscopic observation of the urinary sediment for autofluorescent ceroid granules under ultraviolet illumination.<sup>6</sup>

#### Diagnostic Methods for HPS

Thin sections and whole mounts of platelets were prepared for observation of platelet dense bodies.<sup>7</sup> Platelet rich plasma (PRP) was separated by centrifuging a 9 ml sample of venous blood collected in 1 ml of citrate-citric acid-dextrose anticoagulant (93mM sodium citrate, 7mM citric acid, and 140mM dextrose) at 100g for 20 minutes. Platelets for thin sections were prepared from PRP collected with a plastic pipette from above the buffy coat. One ml was suspended in 0.1% glutaraldehyde and centrifuged at 300g for five minutes. The supernatant was decanted and layered with 3% glutaraldehyde for ten minutes. The supernatant was discarded and 1 ml of fresh 3% glutaraldehyde was added to the bottom which was sent to our laboratory for embedding, sectioning, staining and observation by electron microscopy for the number of dense bodies.

Whole mounts<sup>7</sup> were prepared by placing one drop of PRP on a carbon-stabilized, formvar electron microscopic grid. After incubation for one minute, excess PRP was removed by touching the edge of the grid to filter paper. The grid was washed with a drop of distilled water, and the excess water removed by touching to filter paper. Washing was repeated three times. The grid was dried by waving it in the air. The dried grid was sent to our laboratory for direct observation with an electron microscope. No further treatment of the grid was required before observation, as dense bodies are inherently electron opaque. The diagnosis of HPS was made if the patient's platelets lacked dense bodies.

Five 1 ml aliquots of patient's platelet poor plasma were immediately frozen in liquid nitrogen for determinations of factor VIII procoagulant activity (VIII:C), ristocetin co-factor activity, von Willebrand factor antigen (vWF:Ag), and multimeric structure of von Willebrand factor.

#### Histologic Methods

Tissues fixed in buffered formalin were obtained from patients at autopsy or from surgical specimens of gastrointestinal lesions, granulomatous gingivitis, and lung lesions. In addition, colonic mucosa of patients with and without gastrointestinal lesions were obtained by colonoscopy.

Ceroid was identified thusly: a yellow-brown pigment in unstained sections; an eosinophilic, granular, refractile material in sections stained with hematoxylin and eosin; a

red staining material in sections stained with the Armed Forces Institute of Pathology lipofuscin stain; a periodic acid-Schiff positive material; a yellow-orange autofluorescent material in unstained sections with ultraviolet illumination and by ultrastructural features as an osmiophilic, membrane-bound material in lysosomal structures.<sup>8-11</sup>

A detailed retrospective study of the gynecologic problems of 21 women with HPS was made.

Giemsa banded karyotypes, chromosome breaks and sister chromatid exchanges were determined on five HPS patients and matched controls. HPS heterozygotes were detected by the method of Schallreuter and Witkop.<sup>12</sup> Heterozygote frequency was calculated using the Hardy-Weinberg formula.

#### Results

##### Epidemiologic Study

Platelets from HPS patients lacked dense bodies. Whole mounts of platelets from normal subjects and other types of albinos had 4 to 8 dense bodies per platelet (Fig. 1). When a propositus of a kindred lacked dense

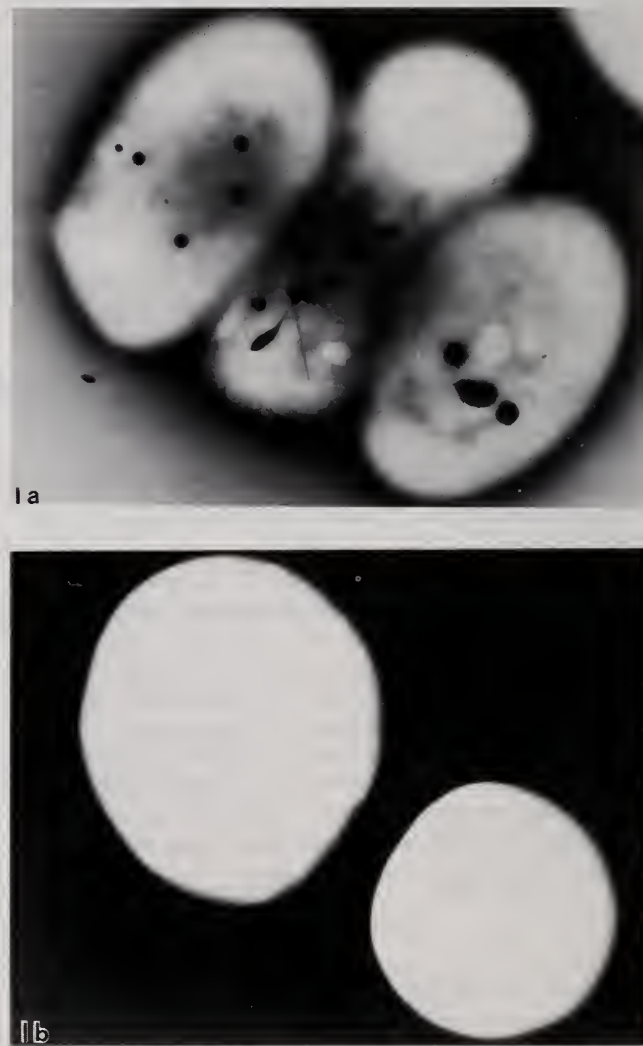


Figure 1. Electron photomicrograph of a whole mount preparation of: (a) normal platelets which on average contain from 4 to 8 dense granules, and (b) platelets from a patient with HPS lacking these organelles.

Mag X 15,000



bodies, all of the examined albino relatives also lacked dense bodies (Table I). When the proband had dense bodies, all examined albino relatives of the proband also had dense bodies. None of these latter albinos had other features of HPS. When a proband of a kindred had a particular type of albinism (ie: HPS, ty-neg OCA, ty-pos OCA, etc.) all of their examined albino relatives had the same type of albinism. Thus it was possible to classify the unexamined and deceased albino relatives of examined and typed albino probands (Table II).

**Table I - Dense body status of 54 albino probands and their 87 albino relatives\***

Number of probands	Total albino relatives	Number of relatives By dense body status	
—38	67	—67	+ 0
+16	20	— 0	+20#

\* +, dense bodies present; —, dense bodies absent

# None of the 36 albinos with dense bodies had ceroid in urine sediment or other evidence of HPS. Patients with ceroid in urine sediment and other evidence of HPS occurred only among the 105 albinos lacking dense bodies.

**Table II - Classification of albinos in the Puerto Rican population**

Albino type	Living albino relatives		Deceased albino relatives typed	Total typed albinos
	Examined typed	Not examined typed		
OCULOCUTANEOUS				
HPS	280	91	113	484
Ty-neg	31	14	3	48
Ty-pos	17	10	1	28
YM	11	3	4	18
Rufous	2	1	0	3
OCULAR				
AROA	7	2	3	12
XOAN	1	0	0	1
Total Typed	349	121	124	594
Unexamined				
	Examined			
	Infants	Living		
	Not	Not Examined		
	Typed	Not Typed		
Total Not Typed	10	77		87
Total Albinos	359	198	124	681

An additional five patients referred to the study were examined but did not have albinism.

## Type of Albinism

Five types of OCA and two types of OA were identified: the Hermansky-Pudlak syndrome (HPS); the white-haired tyrosinase-negative (ty-neg) OCA lacking clinically detectable pigment and its allelic variant, the yellow mutation (ym) OCA; the lightly pigmented tyrosinase-positive (ty-pos) OCA which is non-allelic with ty-neg OCA and the Hermansky-Pudlak Syndrome; the red-haired rufous OCA; the autosomal recessive

ocular albinism (AROA); and the X-linked OA of Nettleship (XOAN) (Table II).

## Prevalence of Albinism

During the five year study period, 681 albinos were identified of which 557 were living and 124 were deceased albino relatives of albino probands. The deceased relatives had died within the period 1940 to 1989 (Table II).

The major portion of HPS patients resided in the northwestern quarter of the island bounded by a line from Barceloneta to Utuado to Playa de Añasco. In 1985, 242 HPS patients were known to be residing in the northwestern portion of the island indicating a minimum prevalence of 1 in 1,793 persons (Table III).

**Table III - Prevalence of HPS albinos in Northwestern Puerto Rico (Area bounded by Barceloneta-Utuado-Playa de Añasco)**

Total HPS albinos living in area in 1985	242
Total estimated population of area 1985*	433,800
Prevalence of HPS in 1985	1:1,793
Approximate prevalence of HPS carrier**	1:22

\* Total population estimated on 1980 census plus 15% increase.

\*\*  $p^2 + 2pq + q^2 = 1$ ;  $p + q = 1$ ;  $q^2 = 0.000558$ ;  $q = 0.0236$ ;  
 $p = 0.976$

Carrier  $2pq = 0.976 \times 0.0236 \times 2 = 0.046$

## Cause of Death

During the period of observation, 47 of 66 HPS subjects (71%) died of causes directly related to the syndrome. Thirty-Two (49%) died from fibrotic restrictive lung disease between the ages of 32 and 65. Eight (12%) died from hemorrhagic episodes from one day of age to 40 years of age; three of these died from post-partum hemorrhage. Seven (10.6%) died from sequelae of granulomatous colitis from 3 to 45 years of age. Three patients had combinations of these disorders as well as renal failure at the time of death. None of the 66 HPS patients died of coronary heart disease. Nineteen persons with HPS died of a variety of causes which appeared to be unrelated to the syndrome, including childhood infections (6), accidents (5), malignancies (5) and tuberculosis (5).

The cause of death among 11 deceased albino relatives of albino probands with types of albinism other than HPS was verified in five instances. Three died of coronary heart disease between ages 25 and 50 years, one child died of pneumonia at one year of age and one died of asthma at ten years of age.

## Genetic Factors

Karyotypes of the five HPS patients were normal. There was no increase in the number of chromosome breaks or sister chromatid exchanges in HPS patients over these in the controls. Hardy-Wineberg calculation of the carrier frequency in the population of northwestern Puerto Rico indicated that 4.6 percent of the population were heterozygotes (Table III). Eight kindreds

showed pseudodominance of the HPS trait with an affected parent and affected children or affected grandparent, affected parent and affected children. In these instances, the affected parent had married a carrier, reflecting the high prevalence of the carriers in the population. In two marriages between HPS spouses, all six children had HPS. All kindreds were compatible with autosomal recessive transmission of HPS.

### Skin Changes and Malignancies

Approximately 80% of HPS albinos over the age of ten years had freckles or lentigines at the time of examination. These were absent in the ty-neg and ym albinos, but freckles and lentigines were present in a few ty-pos albinos. Solar keratoses were present in 21 of 28 ty-neg albinos, 5 of 15 ty-pos albinos and 100 of 203 HPS albinos ten years of age or older. Four of 29 albino students ages 7 to 17 years had solar keratoses. A program of applications of sunblock-15 was instituted for all albino students in 1987. None of 32 albino students examined in 1988-1989 had solar keratoses. Biopsy proven squamous cell carcinoma was found in 27, and basal cell carcinoma in ten HPS and ty-neg albinos. None had melanoma.

### Gynecologic Findings

In 21 women with HPS, a normal age of menarche, menstrual interval and duration were found. Sixty percent (12) complained of menometrorrhagia during each cycle. Forty-six percent (ten) had required a gynecologic surgical procedure as treatment for their abnormally abundant menstrual bleeding patterns. Some had required blood transfusions prophylactically before delivery. No maternal mortalities were noted.

### Ophthalmic Findings

All albinos had nystagmus, diaphanous irides and variable photophobia. Nystagmus was elicited in three HPS albinos only after dark adaptation in lateral gaze. Strabismus was detected in 212 of 247 (86%) ophthalmically untreated HPS patients. Of 188 HPS albinos tested, all but three could read eight and ten point type. None demonstrated binocular vision. Visual acuities in HPS albinos ranged from 20/70 to 20/400. No color vision defects were found on Ishihara testing.

### Granulomatous Enteropathic Disease

Granulomatous enteropathic disease resembling Crohn's disease was confirmed in 22 HPS patients. Thirteen HPS patients had granulomatous enteropathic disease, seven deceased albino siblings had died from sequelae of confirmed granulomatous colitis, two had colitis, restrictive lung disease and kidney failure at the time of death. Two HPS patients had chronic granulomatous gingivitis. The earliest onset of the enteropathic disease was at age three. Most patients developed granulomatous enteropathic disease after 13 years of age. The colitis usually responded poorly to medical treatment and most often, required surgical intervention.

### Pulmonary Findings

Thirty HPS patients ages 14 to 42 had pulmonary

function tests. Fifteen had no evidence of pulmonary restriction, nine had mild restrictive disease, two had moderate restriction, three had severe disease and one had mild obstructive lung disease. The oldest tested HPS patients without evidence of pulmonary restriction was 42 years of age.

### Histologic and Ultrastructural Studies of Autopsy and Biopsy Material

Ceroid accumulated first, and in largest quantities, in the kidney, the reticuloendothelial system, and the liver. Moderate amounts were found in lung, gastrointestinal tract and cardiac muscle, and lesser amounts in other organs. In the kidney, the material accumulated first in the proximal tubular epithelial cells, later in the epithelial cells of the distal and collecting tubules, only a little was found in the glomeruli. Ceroid was absent in the bone marrow in infants two and three years old, was present in some children eight to 15 years old and present in all adults over 20 years of age. The deposits seen by electron microscopy were within membrane-bound lysosomal-like structures. The majority of the material was amorphous with an occasional deposit showing a curvilinear or finger print pattern as seen in forms of neuronal ceroid-lipofuscinoses.

### Evidence of a Hemorrhagic Diathesis in HPS

Multiple bruises were present at the time of the clinical examination in 85 percent of HPS patients and were absent in albinos of other types with the exception of three ty-neg patients. Bleeding time of HPS patients varied from six minutes to over 20 minutes. Bleeding time in approximately one-fourth of the HPS patients tested (6/26) were within the normal range (5-9 minutes). Platelet counts were normal except in the rare event when another intervening cause was also present. Seven of 46 HPS patients tested were found to have von Willebrand disease type I in addition to their platelet defect from HPS.

### HPS Platelet Function

HPS platelets lacked inherently electron opaque dense bodies, the storage sites for adenine nucleotides and serotonin destined for secretion in normal human platelets. Biochemical evaluation revealed less than 10% of the normal levels of ADP and 5-hydroxytryptamine in HPS cells. However, the enzymes required for synthesis of thromboxane  $A_2$  ( $TxA_2$ ) were present. Platelet-rich plasma combined in equal volumes with platelet-rich plasma from normal donors following ingestion of aspirin, which blocks  $TxA_2$  synthesis, developed irreversible aggregation when stirred with agonists on a platelet aggregometer. Similar concentrations of agonists produced only a single, completely reversible wave of response when stirred with HPS platelets alone or aspirin-treated control platelets alone. Thus the  $TxA_2$  formed in HPS platelets is important, and may serve as an alternate pathway to secure hemostasis in the storage-pool deficient HPS platelets.

Patients with HPS after treatment with aspirin were unable to generate  $TxA_2$ . Epinephrine alone and



thrombin alone at concentrations which aggregate samples of normal platelets failed to cause aggregation of HPS cells. However, HPS platelets primed by adding epinephrine to the sample first restored their sensitivity. Subsequent addition of thrombin or another agonist to the epinephrine-primed platelets resulted in their irreversible aggregation without secretion of stored products or synthesis of  $\text{TxA}_2$ . Thus, HPS platelets have two alternate pathways of aggregation, thromboxane  $\text{A}_2$  synthesis and membrane modulation by epinephrine, to help bypass the functional deficiency imposed on HPS platelets by storage pool deficiency.

### Discussion

Five types of OCA and two types of OA were found among albinos in Puerto Rico. Approximately five of every six albinos had HPS. HPS has been observed in 19 diverse ethnic populations.<sup>1</sup> The prevalence of HPS in northwestern Puerto Rico of approximately 1 in 1,800 persons is the highest of any population yet reported. In this area of Puerto Rico, approximately 1 in 22 persons carry the gene for HPS. This high prevalence of HPS in northwestern Puerto Rico probably represents a founder effect early in the history of the island.

HPS albinos may phenotypically resemble any other type of OCA or OA albino. Thus the pigment phenotype is not a reliable diagnostic feature of HPS.<sup>5</sup> The urinary excretion of ceroid is variable in HPS patients,<sup>6</sup> and not all HPS patients develop pulmonary fibrosis, granulomatous enteropathic disease or kidney failure. Carefully conducted platelet aggregation tests with HPS platelet rich plasma (PRP) will usually elicit an abnormal response with absence of the secondary wave of irreversible aggregation.<sup>7, 8, 13-17</sup> However, normal nephelometric responses have been noted in initial tests on PRP from HPS patients.<sup>7, 18</sup> Further, abnormal nephelometric responses identical to those of HPS patients may occur in subjects without storage-pool deficient platelets following ingestion of drugs such as aspirin and indomethacin that interfere with cyclo-oxygenase.<sup>13-17</sup> HPS is best diagnosed by a deficiency of platelet dense bodies observed by electron microscopy in whole mounts of PRP or in thin sections of glutaraldehyde fixed platelets.<sup>7</sup>

The basic defect responsible for the absence of dense bodies in platelets from patients with HPS and relationship to other characteristic features of the syndrome remains obscure. The virtual absence of dense bodies clearly affects the function of platelets *in vitro* and *in vivo*. Despite the demonstrable dysfunction, many HPS patients are almost symptom-free and have normal bleeding times. Others, demonstrating similar levels of abnormal platelet activity *in vitro*, have life-long histories of bruising, mucous membrane bleeding and life-threatening hemorrhagic complications. Mild von Willebrand factor deficiency may be a complicating factor in some HPS patients, but in others, the platelet storage pool deficiency seems to be the only basis for the hemorrhagic disease. The ability of HPS platelets to generate thromboxane  $\text{A}_2$  and aggregate irreversibly to agonists in the presence of epinephrine may compensate for the storage pool deficiency.<sup>16, 17</sup>

Detailed ophthalmic studies made on 22 HPS albinos

from this project extended the findings in the field study.<sup>19, 20</sup> All had diaphanous irides, nystagmus and varying degrees of photophobia. Two had moderate amounts of pigment in the irides, 12 had minimal pigment and six had no visible pigment. The best corrected Snellen acuities ranged from 20/60 to 20/400. The best corrected visual acuity in 82.5% of the eyes was 20/200 or worse. Astigmatism greater than two diopters was found in 90%. Compound hyperopic astigmatism was the most frequent type (42.5%). Twelve patients had esotropia, six had exotropia and the three had hypertropia in addition to horizontal strabismus. None had stereoacuity and all 11 of the patients tested had asymmetric visually evoked potentials indicative of abnormal crossing of the optic tracts at the chiasm. All eyes had complete lack of foveal development, 80% had an abnormal pattern of macular blood vessels and only one eye showed any melanin in the macula.

Evidence that HPS is a lysosomal ceroid storage disease was investigated in a study of 23 HPS patients with ceroid storage and 27 without storage disease.<sup>6</sup> Patients were evaluated for their urinary output of ceroid and dolichols which are derived from lysosomal membranes<sup>21</sup> and compared to normal controls. As a group, all HPA patients had significantly higher urinary output of dolichols than controls. Patients with ceroid storage disease had the highest excretion of dolichols. However, three patients with ceroid storage disease had normal dolichol levels. While ceroid granules in urine sediment were found in asymptomatic children as young as five years of age, the frequency of this finding increased with age and the onset of symptomatic storage disease. Patients fed a diet of 60 percent polyunsaturated fat for two weeks and then a diet of 60 percent saturated fat for two weeks showed no significant variations in daily ceroid output strongly suggesting that ceroid in HPS is not derived from dietary polyunsaturated fats.

The colonic histologic changes in these patients<sup>11, 25, 26</sup> indicated that the earliest changes were plaques of ceroid seen electron microscopically in the lamina propria of asymptomatic patients. Symptomatic patients had non-necrotic, non-caseous granulomas containing ceroid in the submucosa. Advanced lesions had frank ulceration, necrosis, fistulas and perforations. Granulomas involved both small and large bowel segments.

The histological and ultrastructural findings of tissue lesions and distribution of ceroid deposits in HPS patients in this study was similar to those found by others.<sup>3, 18, 22-24</sup> Ceroid was stored intracellularly in lysosomes.<sup>8, 9, 11, 25, 26</sup> Ceroid accumulated first in largest quantities in the proximal tubules of the kidney, in the reticuloendothelial system, and in the liver.<sup>5, 8, 9, 11, 25, 26</sup> Moderate amounts were found in lungs, gastrointestinal tract, and cardiac muscle and lesser amounts in other organs. The accumulation of ceroid is, at least in part, age dependent. There is no known degradative biochemical pathway for ceroid.<sup>21</sup> Ceroid is thought to be eliminated from cells by exocytosis.<sup>11, 21, 25</sup> The exact chemical composition of ceroid which accumulates in HPS is unknown. It shares with neuronal ceroid-lipofuscin the features of yellow autofluorescence under ultraviolet illumination, stains acid fast and positive with the Armed

Forces Institute of Pathology lipofuscin stain. It is insoluble in strong acids and alkalis and has ultrastructural similarities with ceroid in the ceroid-lipofuscin diseases such as Batten disease.<sup>11, 21, 25, 26</sup> HPS shares with the neuronal ceroid-lipofuscinoses an increased excretion of urinary dolichols indicative of the lysosomal storage defect in these conditions.<sup>21</sup>

It has been proposed that activation of pulmonary alveolar cells to produce mesenchymal growth factors is an initial step in the pathogenesis of idiopathic pulmonary fibrosis.<sup>27</sup> There is controversy concerning the cell type which initiates the response that culminates in the development of the disease.<sup>27</sup> The inability to predict which patients will develop the disease makes it difficult to investigate the initial stage of the disorder.<sup>28</sup> HPS patients can be identified in childhood. Nearly all will develop pulmonary fibrosis by 45 years of age.

Seven of 12 young adult HPS patients ages 17 to 29 years without significant defects in pulmonary function tests had normal differential counts of lavaged cells,<sup>29</sup> but there were large quantities of ceroid in the alveolar macrophages.<sup>25</sup> These seven patients had increased levels of platelet derived growth factor (HPS -  $27 \pm 42$  units; normal controls undetectable) in the bronchoalveolar lavage, indicating that the elevation of growth factor precedes the fibrosis.<sup>29</sup>

Abnormalities in the immune system had been proposed in the pathogenesis of Crohn's disease<sup>30</sup> and idiopathic pulmonary fibrosis.<sup>27</sup> A detailed assessment of 15 HPS patients,<sup>31</sup> four with granulomatous enteropathic disease, found no abnormalities in immunoglobulin levels, complement, lymphocyte subsets, natural killer and lymphokine-activated cytotoxicity, mixed lymphocyte responses, lectin-induced transformation, neutrophil function including luminal-dependent chemiluminescence, chemotaxis and aggregation. There was no lymphocyte proliferative response to an isolated ceroid preparation.

It has been reported that HPS patients have increased chromosomal breakage.<sup>32</sup> It has been proposed that albinos in general are susceptible to develop storage pool deficient platelets and ceroid storage<sup>32</sup> and that HPS is due to mutations of three closely linked genes, each determining the three features of the triad.<sup>33</sup> We have found no cytogenetic abnormalities in HPS. Except for storage pool deficient platelets in Chediak-Higashi disease, albinos other than HPS, do not develop platelet and ceroid defects. The genetic evidence and concordant platelet findings indicate that the HPS triad is determined by a single gene mutation.

**Resumen:** Cinco tipos de albinismo oculo-cutáneo y dos tipos de albinismo ocular se encontraron entre 349 albinos puertorriqueños examinados. El tipo de albinismo más prevalente fue el tipo conocido como el síndrome de Hermansky y Pudlak (SHP). El SHP se observó en 5 de cada 6 albinos de Puerto Rico. La prevalencia de SHP en la parte noroeste de la isla fue uno en 1,800 personas, y aproximadamente uno en 22 son portadores del gene. Albinos con SHP se asemejan fenotípicamente a otros de tipos de albinismo oculocutáneo y ocular.

El SHP es una tríada autosomal de herencia recesiva, compuesta por un tirosinasa-positivo tipo de albinismo, sangramiento excesivo a consecuencia de deficiencia en la capacidad de almacenamiento de las plaquetas, deficiencia en la función de las mismas y acumulación de ceroides en los tejidos. El diagnóstico del SHP se hace por medio de una microscopía electrónica basada en la ausencia de cuerpos densos en las plaquetas sanguíneas.

La acumulación de ceroides en los tejidos es asociada con las enfermedades fibrosis restrictivas del pulmón y enteropática granulomatosa. La causa principal de muerte en personas con SHP fue la fibrosis restrictiva del pulmón entre los 32 y 65 años de edad, seguida por episodios hemorrágicos y secuela de la enfermedad enteropática granulomatosa. Esta enfermedad enteropática se asemeja a la enfermedad de Crohn, la cual generalmente se manifiesta después de los 13 años de edad, siendo refractaria a los tratamientos médicos habituales y requiriendo intervención quirúrgica. La menometrorragia fue común en mujeres con el SHP. No hemos encontrado deficiencia inmunitaria en pacientes con SHP. La mayoría de los albinos con este síndrome tienen una agudeza visual no mayor de 20/200, en consecuencia se les considera legalmente ciegos. Los albinos en general no poseen visión binocular, debido al cruce anormal del tracto en el quiasma óptico. Se requieren estudios posteriores para explicar la patogénesis del síndrome.

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**"He flourished during the first half of the 20th century."**

# Primary Lateral Sclerosis: A Distinct Clinical Entity in Patients with Chronic Spastic Paraparesis\*

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**Summary:** The development of neurologic deficits confined to the corticospinal tracts has been referred as Primary Lateral Sclerosis (PLS). Through the years, this diagnosis has remained uncertain. In this study we describe seven patients with chronic involvement of the pyramidal system. Two of these patients had serologic evidence of human T-lymphotrophic virus type I infection, one patient had multiple sclerosis and in four patients the clinical diagnosis of PLS was made. The clinical characteristics and diagnostic studies of these patients are presented. A review of the literature with emphasis in the differential diagnosis and a proposed workup for patients with chronic spastic paraparesis are made. This study provides supporting evidence in favor of the clinical entity of PLS.

In 1875 Erb defined a clinical entity in adults, with non inherited bilateral corticospinal tract dysfunction developing a slowly progressive spastic paraparesis without sensory deficits. It was named primary lateral sclerosis (PLS). According to Erb's original description, no dysfunction related to any part of the nervous system except the pyramidal tracts is allowed when a diagnosis of PLS is made.<sup>1</sup> The validity of the diagnosis of PLS before 1905 has been questioned since myelography was not available and the diagnosis of cervical spondylosis was not recognized.<sup>2</sup> In 1977, Fisher published the first case report with pathologic evidence of PLS.<sup>3</sup> On autopsy there were no abnormalities of the cerebral hemispheres or brainstem but in the spinal cord from the cervical to the sacral segments there were well demarcated zones of selective demyelination in the lateral corticospinal tracts bilaterally. The anterior horn cells were normal. Finally, in 1988, Younger and Rowland described six living patients with PLS.<sup>4</sup>

## Subjects and Methods

In this study seven patients between the ages of 28 to 66 years old presented a chronic onset of gait difficulties and lower extremities weakness. The duration of symptoms varied from eight to thirty-six months, as shown in

Table 1. There was no family history of similar disease. Four patients were chronic smokers and patient 7 had history of intravenous drug abuse for thirteen years. The second patient had been exposed to organophosphates due to his work as a farmer.

Many patients had sensory complaints although objective sensory loss was present only in patient 3 who on examination had a sensory deficit to principle at the thoracic level with a spastic bladder. The patient could have suffered an initial vascular or infectious event but in a term of thirty-six months he presented worsening of the neurologic signs to a spastic paraparesis which is unusual in vascular or infectious events. All patients had a spastic paraparesis except for patient 7 who presented a spastic quadriparesis and patient 5 who had a spastic left-sided hemiparesis and evidence of bilateral corticospinal tract disease. All patients had hyperactive deep tendon reflexes and/or Babinski signs. These findings are summarized in Table 2.

## Results

The diagnostic studies done are shown in Table 3. Electromyography revealed peripheral neuropathies with evidence of muscle denervation in five of the seven patients. However, these findings were nonspecific. None of our patients had electrophysiological evidence of lower motor neuron disease. Patients 6 and 7 had antibodies detected in serum and in cerebrospinal fluid against human T-lymphotrophic virus type I (HTLV-I) which is isolated in eighty percent of reported cases of tropical spastic paraparesis. Serum human immunodeficiency virus (HIV), long chain free fatty acids, circumoval test and lead and mercury levels were negative in those patients tested. All the patients had normal serum vitamin B-12 and folate levels. Lumbar puncture results including cellularity and cytology tests were normal except in two patients that presented high cerebrospinal fluid protein levels. Only one patient had oligoclonal bands in cerebrospinal fluid with increased myelin basic protein levels (patients 5). In this patient, magnetic resonance imaging (MRI) studies revealed numerous focal hyperintense white matter lesions in both cerebral hemispheres and spinal cord compatible with multiple sclerosis. On complete myelographic and computed tomogram studies two patients had cervical osteophytes without compression of spinal cord. These radiographic findings did not explain the neurologic deficits. In the remaining first four patients, the diagnosis of

\* This study was presented in the American College of Physicians, Puerto Rico Chapter, Annual Meeting on October 28, 1989, San Juan, Puerto Rico.

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Table 1 History Profile of V.A.H. Patients with Chronic Spastic Paraparesis

	1	2	3	4	5	6	7
Duration of symptoms (mo)	24	24	36	8	36	9	12
Family history	Non-contributory	Non-contributory	Non-contributory	Non-contributory	Non-contributory	Non-contributory	Non-contributory
Toxic habits	None	Smoking	None	None	Smoking	Smoking, Alcohol abuse	Smoking, Alcohol abuse, IV drug abuse
Sensory Complaints	None	Numbness and tightness of legs	Numbness and tingling of legs	Cramps in legs	None	Paresthesias in legs	None
Past History	None	Organophosphates exposure	Neurodermatitis, Fibromyositis	Gonorrhea	Head trauma, cervical ribs, Lt vertebral fracture, cholelithiasis	PUD	PUD

Table 2 Characteristics of V.A.H. Patients with Chronic Spastic Paraparesis

	1	2	3	4	5	6	7
Age (y)	63	51	40	32	28	66	58
Sensation	Intact	(+) Romberg	(+) Romberg sensory level T-10	Intact	Intact	Intact	Intact
Bladder and bowel function	Intact	Urinary incontinence	Spastic bladder	Intact	Intact	Intact	Intact
Motor system	Arms: 5/5 Lt Leg: 4/5	Arms: 5/5 Legs: 4/5	Arms: 5/5 Legs: 4/5	Arms: 5/5 Legs: 5/5	Lt Arm/Leg: 4/5 Rt Arm/Leg: 5/5	Arms: 5/5 Legs: 3/5	Arms: 4/5 Legs: 3/5
Cerebellar findings	Intact	Intact	Unable to do tandem gait	Intact	Intact	Intact	Intact
Cranial nerves	Intact	Intact	Intact	Intact	Intact	Intact	Intact
Deep tendon reflexes	Hyperactive with bilateral Babinski	Hyperactive with bilateral Babinski	Hyperactive with bilateral Babinski	Hyperactive with bilateral Babinski	Hyperactive with bilateral Babinski	Hyperactive	Hyperactive

Table 3 Laboratory Results of V.A.H. Patients with Chronic Spastic Paraparesis

	1	2	3	4	5	6	7
EMG-NCV	Demyelinating disease	Peripheral neuropathy	Peripheral neuropathy	Normal	Normal	Burst of (+) waves	(+) waves in legs
Protein electrophoresis	Normal	Normal	Normal	Normal	Normal	Normal	Polyclonal increase in gamma globulin
Serum HTLV-I	NR	NR	NR	NR	NR	(+) in CSF and serum	(+) in serum
Serum HIV	NR	NR	NR	NR	NR	NR	NR
LC-FFA	ND	ND	Negative	ND	Negative	ND	ND
Serum circum-oval	Negative	Negative	Negative	ND	ND	Negative	Negative
Pb-Mg levels	ND	ND	Negative	Negative	ND	ND	ND
Cells							
Cells (WBC/ $\mu$ m <sup>3</sup> )	0	0	0	1	4	0	0
Protein (mg/dl)	94	32	42	33	60	31	43
Oligoclonal bands	None	None	None	None	2	None	None
Cytology		Negative	Negative			Negative	Negative
Myelogram-CT	Spinal cord narrowing at C <sub>3-4</sub> and C <sub>4-5</sub>	L <sub>4-5</sub> degenerative changes	Negative	Negative	Normal	Normal	C <sub>3-4</sub> posterior osteophytes
Brain MRI	Old left basal ganglia infarction	ND	ND	Normal	White matter lesions and Rt ventricle enlargement	Normal	Normal
Cervical MRI	Normal	Normal	ND	ND	White matter hyperintense lesions	Normal	As myelogram

ND = Not Done

primary Lateral sclerosis was made after excluding all diagnostic possibilities.

An additional living patient with paraparesis, severe spasticity and urinary incontinence was found to have tropical spastic paraparesis since this report was written for publication.

### Discussion

The differential diagnosis of spastic paraparesis includes compressive lesions, hereditary causes, central nervous system infectious or vascular diseases and unknown causes. Cervical spondylosis, foramen magnum tumors and Chiari malformations are the most common compressive lesions.<sup>5-6</sup> Familial spastic paraparesis including adrenoleukodystrophy and multisystem diseases such as spinocerebellar degeneration and Shy-Drager syndrome usually have an hereditary basis.<sup>4, 7</sup> Neurosyphilis, tropical spastic paraparesis and HIV vacuolar myelopathy have all an infectious origin.<sup>8-10</sup> Multiple sclerosis, syringomyelia, lathyrism and lacunar disease can produce spastic paraparesis in young and middle-aged patients.<sup>11-12</sup>

It is very important to exclude treatable causes of chronic spastic paraparesis. For this reason, the following diagnostic studies, as shown in Table 4, are proposed in these patients: complete myelograms or magnetic resonance imaging of the brain and spinal cord; electromyogram and nerve conduction velocity studies; cerebrospinal fluid examination for cytology, VDRL, multiple sclerosis panel, HIV and HTLV-I; serum HIV; serum HTLV-I; serum long chain free fatty acids; serum circumoval test and serum cortisol levels among others.

If all the alternative diagnosis are properly excluded, it is possible to make the clinical diagnosis of PLS with a high degree of accuracy. This is the case in the first four patients in our study. Whether PLS is a limited form of amyotrophic lateral sclerosis remains to be proven. Anterior horn cells have been spared pathologically in all reported autopsy cases of PLS. The cause of PLS is unknown and there is no known effective therapy. It is a challenge for the future to understand its pathogenesis

and develop a rational therapy. This study provides supportive evidence in favor of the clinical entity of PLS and expands previous reports establishing the possibility of making the antemortem diagnosis with precision.

**Resumen:** La aparición de signos neurológicos confinados al tracto piramidal se conoce como esclerosis lateral primaria. A través de los años, este diagnóstico ha sido cuestionado. En este estudio se describen siete pacientes con daño crónico del sistema piramidal. Dos de estos pacientes tenían evidencia serológica de infección con el virus humano T-linfotrópico tipo I. Un paciente tenía esclerosis múltiple y en cuatro pacientes el diagnóstico de esclerosis lateral primaria fue hecho. Las características clínicas y estudios diagnósticos de estos pacientes son presentados, incluyendo una revisión de la literatura con énfasis en el diagnóstico diferencial de paraparesis espástica crónica. Este estudio provee evidencia a favor del diagnóstico de esclerosis lateral primaria como una entidad clínica.

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Table 4

#### Proposed Workup for Patients with Chronic Spastic Paraparesis

1. Cerebrospinal fluid examination including cytology, VDRL, MS panel, HIV and HTLV-I
2. SSEP
3. CT-myelogram.
4. Cervical MRI
5. Brain MRI (head CT scan)
6. EMG-NCV
7. Very long chain free fatty acids
8. Serum and CSF HIV
9. Serum and CSF HTLV-I
10. Serum circumoval test
11. Serum lead and mercury levels
12. Serum protein electrophoresis
13. Serum vitamin B<sub>12</sub> levels
14. Serum folate levels
15. Serum cortisol levels



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# Misreporting of Maternal Mortality in Puerto Rico

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**Summary:** Maternal mortality (MM) continues to be a problem that plagues many developed and underdeveloped countries around the world. It has been estimated that the minimum amount of underreporting in the U.S. to be 20%, resulting in MM rates that may be substantially higher than reported. The national goal for the MM for the year 1990 has been set at 5/100,000, and at the present trend it is expected that this may be achieved among the white population, but not among minorities. P.R. reported a maternal mortality rate of 5/100,000 in 1975. It was suspected that such a low rate was due to underreporting, a study was undertaken to investigate that possibility. The results indicated that there was severe underreporting of maternal deaths during 1978 = 79. Recently, there has been a growing concern that the level of underreporting in PR continues to be high. Since there has been no evidence that the surveillance has improved, the Dept. of Health requested from the Dept. of Ob-Gyn of the University of Puerto Rico Medical School and the Dept. of Maternal and Child Health to conduct a study to find out if the previous findings held true for recent years. The study was based on the review of selected medical records corresponding to deaths of women of childbearing age whose causes of death, as coded in the death certificate, were considered as having a high probability of masking a misreported maternal death. It was decided to investigate those deaths occurring in 1982, to see if the results of the previous study had caused any impact on the surveillance of maternal deaths in Puerto Rico.

**M**aternal mortality continues to be a problem that plagues many developed and underdeveloped countries around the world.<sup>1, 2</sup> Adding to its severity is the fact that this condition is notoriously underreported.<sup>2, 3, 4</sup> It has been estimated that the minimum amount of underreporting in the United States would be 20%,<sup>5</sup> resulting in maternal mortality rates that may be substantially higher than reported.

The national goal for the maternal mortality for the year 1990 has been set at 5 per 100,000, and at the present rate and trend it is expected that this may be achieved among the white population, but not among the black and other minorities.<sup>6</sup> Puerto Rico reported a maternal mortality rate of 5 per 100,000 in the year 1975. It was suspected at the time that such a low rate was due to underreporting, and a study was undertaken under the auspices of the Commonwealth of Puerto Rico Department of Health and the Center for Disease

Control to investigate that possibility.<sup>7</sup> The results definitely indicated that there was severe underreporting of maternal deaths during the years 1978 and 1979 due to errors of coding at the office of vital statistics, erroneous filling out of death certificates by physicians, and inadequate identification of cases.

In recent years, there has been a growing concern that the level of underreporting of maternal deaths in Puerto Rico continues to be high, since there has been no evidence that the surveillance had improved. For these reasons, the Commonwealth of Puerto Rico Department of Health requested from the Department of Obstetrics and Gynecology of the University of Puerto Rico School of Medicine and the Department of Maternal and Child Health of the University of Puerto Rico School of Public Health to conduct a similar study to find out if the previous findings held true for more recent years.

The study was based on the review of selected medical records corresponding to deaths of women and childbearing age whose causes of death, as coded in the death certificate, were considered as having a high probability of masking a misreported maternal death. It was decided to investigate those deaths occurring on 1982, to see if the results of the previous study carried out on 1981<sup>7</sup> had caused any impact on the surveillance of maternal deaths in Puerto Rico. It was also expected that studying deaths of more recent years would have increased the non-response rate among health care facilities by denying access to medical records.

## Materials and Methods

During the year of 1982 a total of 886 deaths occurred among women between ages 10 and 49 years, being this age group the one that would include most of the female pregnant population. From this total, 165 deaths attributed to external causes were initially discarded from the study, since the probability of these being maternal deaths was very small. This initial screening reduced the number of deaths under study of 721 deaths.

A group of five obstetricians reviewed a copy of the International Classification of Diseases, Ninth revision (ICD-9), to identify those causes of death that they would consider of low probability of being erroneously assigned to a maternal death. The ICD-9 was the same version used on 1982 for the coding of death certificates. Using the codes corresponding to the selected causes of death, 218 deaths were eliminated from the study.

A list of death certificate numbers assigned to deaths attributed to the remaining causes of death was generated from a copy of the computerized death registry data for 1982, which is kept at the Medical Sciences Computing

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Center. Copies of these 503 death certificates were obtained from the Demographic Registry of the Department of Health, and were reviewed by the group of obstetricians, who reached a consensus about which of the certificates had a high probability of not belonging to a maternal death. Twenty-one death certificates were eliminated from the study after this review. Overall, the initial screening procedures yielded a potential 482 deaths whose medical records would be reviewed. Eleven of these deaths did not specify the place of death and another eighty-four reported that the death had occurred at home. These 95 death certificates contained no further information that would permit the investigation of the circumstances of their deaths. Although these records were not revised they might have increased the yield.

An attempt to locate the medical records and/or autopsy reports of the remaining 387 deaths was initiated after requesting a letter of support from the Secretary of Health to be sent directly to those health care facilities where the deaths under study had occurred or where the autopsy was performed. Forty-seven deaths occurred on health-facilities that refused to cooperate with the study. Each of the institutions that offered their cooperation were visited to review the medical records and/or autopsy reports belonging to the remaining 340 death certificates. Information about 274 of these was available.

The procedure for the identification of maternal deaths was the following. Each record was reviewed at each of the health facilities by a fourth-year medical student looking for any information that would indicate if the deceased had been pregnant at any time during the date of death. To minimize the probability of error in the determination of this time interval, a computer generated list was provide to each student. This list showed the beginning of the ninety-days period for each possible date of death (365 possibilities) for the year 1982. Each student was trained in the use of this list before he/she was sent to the field. If the deceased had not been pregnant during the critical period, no more information was collected. If the information on the record stated that the patient had been pregnant at any time during the 90 days prior to the date of death, then the record was reviewed in more detail and the information was recorded on a worksheet developed for these purposes by the American College of Obstetricians and Gynecologists. To insure that this procedure was followed correctly, a systematic random sample (one out of every three) was obtained from a list of death certificates stratified by place of occurrence of death after the exclusion of deaths previously discard from the study. Medical records belonging to this sample of death certificates were reveiued a second time by a medical clerk, who found that none of the deaths in the sample had been incorrectly discarded by the medical students. If there was any indication in the death certificate or in the medical record that an autopsy had been done, additional efforts were made to locate the corresponding report.

Information from the worksheet was then reviewed by an obstetrician with experience in the operation of maternal mortality committees to determine which deaths were related to pregnancy. A maternal death was defined as a death due to any cause related or aggravated

by pregnancy or by its management occurring during pregnancy or within the 90 days prior to its determination. Different time intervals after pregnancy termination have been recommended as the best for purposes of defining a maternal death.<sup>1, 8</sup> Our choice of the 90 days interval was a compromise between our goal of detecting as many maternal deaths as possible and our limitations of personnel and other resources. Also, the previous study<sup>7</sup> had shown that most maternal deaths could be detected using this definition.

Results and Discussion

A total of 28 maternal deaths were identified in our study (Table I), and only 8 of them had been classified as such by the Department of Health.<sup>9</sup> Since our study did not review all records belonging to all deaths occurring during 1982, our results reveal a minimum of 71.4% (20/28) of underreporting. The significance of this findings lies in the impact upon the maternal mortality ratio (Table II). Our results indicate that this ratio was 40.4 per 10,000 live births, 3.5 times higher than what vital statistics show for that year.

When the maternal deaths were classified according to their potential method of identification, we find that only three of the twenty misreported deaths (15%) could have been identified by information provided by the death certificate. The remaining seventeen could only be detected by reviewing medical records.

From the total 28 deaths identified, the exact number of days after termination of pregnancy was obtained for 24. Medical records belonging to the other four deaths

Table I  
Maternal Deaths and Mortality Rates Per 100,000 Live-Births by Surveillance Method.  
Maternal Mortality Study, Puerto Rico 1982

Method	Deaths	Rate
Vital statistics (*)	8	11.5
Maternal mortality Study	28	40.4

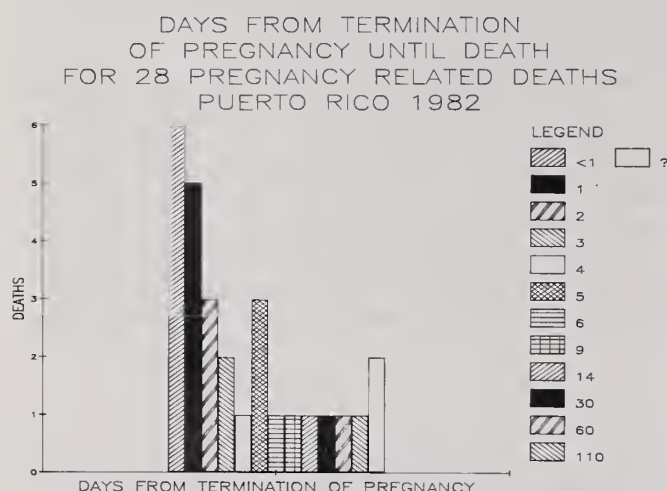
\* Vital Statistics Annual Report, 1982. Department of Health.

Table II  
Number and Proportion of Maternal Deaths by Method of Identification.  
Maternal Mortality Study, Puerto Rico 1982

	Number	Percent
Vital statistics	8	28.6
Review of death certificates	3	10.7
Review of medical records	17	60.7
Total	28	100

contained information that permitted to determine that the decease had occurred within 90 days from the time of pregnancy termination but did not specify the exact date of termination. Figure 1 shows the distribution of this changes by number of days after termination of pregnancy on which death occurred. Most of these deaths happened on the same day of pregnancy termination or before the pregnancy was terminated.

The results of this study are very similar to a previous investigation, when the percentage of misreporting was found to be 72.6% (45/62) for the 1978-79 period.<sup>7</sup> Both studies provide a similar estimate even when the research methods had major differences in the procedures for the selection of death certificates that might results in misreported maternal deaths and in the procedures for the misreporting of maternal deaths was significant during the years following the initial study, and that it probably continues to this day.



### Recommendations

The improvement of maternal mortality reporting in Puerto Rico should be based on both short and long-term strategies. A short term strategy would be the inclusion of an item in the death certificate asking if the deceased was pregnant at any time during the twelve months preceding her death. This strategy has significantly improved maternal mortality surveillance in several areas of the United States.<sup>13</sup> A variation of this would be to provide a box on the death certificate for the doctor to register the termination of the pregnancy within one year.

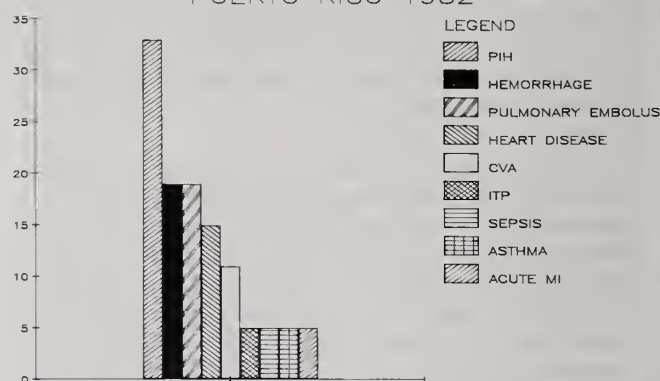
Another short-term strategy would be the creation of an official Commonwealth Committee on maternal mortality. Many local state maternal mortality committees have been formed in the United States, some of them dating back to the 1940's and 1950's.<sup>10, 11, 12</sup> These committees have played a major role in the evolution of adequate surveillance mechanisms of pregnancy-related deaths.<sup>3, 10, 11, 12</sup>

The development of computerized informations systems have made possible to handle huge amount of information with relative ease. Some studies related to

maternal mortality have relied on computerized linkage between birth and death registries.<sup>4, 11</sup> This method might be implemented to supplement other surveillance activities developed by a maternal mortality committee. A limitation of this method is that it cannot detect deaths associated with pregnancies that do not terminate in delivery such as abortion, ectopic or molar pregnancy.

Many maternal deaths were misreported on 1978, 1979,<sup>7</sup> and 1982 because the physician did not in fill correctly the information related to cause of death. Medical schools, residency programs, and continuing medical education activities should emphasize the importance of the correct reporting of the causes of death on the death certificate concurrent with adequate coding and above all clear legible handwriting. On the long-run this strategy would improve maternal mortality surveillance.

PREGNANCY RELATED MORTALITY RATIOS  
FOR SELECTED MEDICAL RISK FACTORS  
BY METHOD OF SURVEILLANCE  
PUERTO RICO 1982



### Conclusion

The degree of misreporting of maternal deaths in Puerto Rico is very high. Measures to improve surveillance of these deaths should be taken promptly. These should include the modification of the death certificate to obtain information about the time of last pregnancy termination, the institution of a Commonwealth maternal mortality committee, the establishment of birth and death certificate linkage and statistics, and training physicians, medical students, and clerical personnel on the correct filling of death certificates and codification.

To increase the yield of pregnancy related deaths reporting, all women should have a complete obstetrical-gynecological history and evaluation during all hospitalizations.

The training of vital statistics personnel should be oriented to recognize these cases with the purpose of decreasing errors in codification and thus decrease underreporting.

The principal limitation of the study lies in the impossibility of examining every case of the sample producing a



lower yield, than was anticipated. This record review is highly skewed by the medico-legal problems involved and the statute of limitation for studying of records. The limitation of time, facilities, man power and fiscal constraints are also very important limiting factors.

A preliminary review of the 1983 death certificates of women of reproductive age has demonstrated a 50% increase in the reporting of pregnancy related death even without medical and autopsy records surveillance.

If our recommendations are followed and appropriate funding is available, this study should be conducted on a yearly basis.

This study also included an evaluation of the different risk factors associated with pregnancy related death which will be the subject of a separate publication.

The latest statistics available are those of 1986. These report 10 maternal deaths in 63,551 births yielding a Maternal Mortality Rate of 15.7. Is this a reflexion of better reporting? Have our limited efforts started to take effect? Has physicians awareness improved? Will the inclusion of the pregnancy identification box in the death certificate help in the identification of these cases? These and many other questions remain unanswered, but we hope to approach them in a future study.

**Resumen:** La mortalidad materna (MM) continúa siendo un problema serio en muchos países desarrollados y sub-desarrollados. Se estima que existe un sinúmero de sub-registro en Estados Unidos de 20%, resultando esto en tasas que serán substancialmente mayores que las reportadas. La meta nacional de MM para el año 1990 ha sido fijada en 5/100,000, y se espera que se pueda llegar a dicha meta entre la población blanca pero no en las minorías. Puerto Rico registró una tasa de MM de 5/100,000 en 1975. Se sospechó que esta tasa tan baja se debió a un sub-registro, y se llevó a cabo un estudio para investigar esta posibilidad. Los resultados indicaron que existió un severo sub-registro en 1978 y 1979. Recientemente surgió la preocupación que dicha situación continuase. Como no había evidencia que el registro había mejorado, el Departamento de Salud solicitó del Departamento de Obstetricia y Ginecología de la Escuela de Medicina de la Universidad de Puerto Rico y el Departamento de Salud Materno-Fetal que llevaran a cabo otro estudio para verificar los hallazgos. El estudio se basó en un estudio de expedientes médicos seleccionados correspondiendo a muertes de mujeres en edad reproductiva cuya causa de muerte, según codificados en el certificado de defunción, fueron consideradas como teniendo una alta probabilidad de ser un caso de sub-registro de muerte materna. Se decidió investigar las muertes del 1982, a ver si los resultados del estudio anterior habían causado algún impacto en el registro de MM en Puerto Rico.

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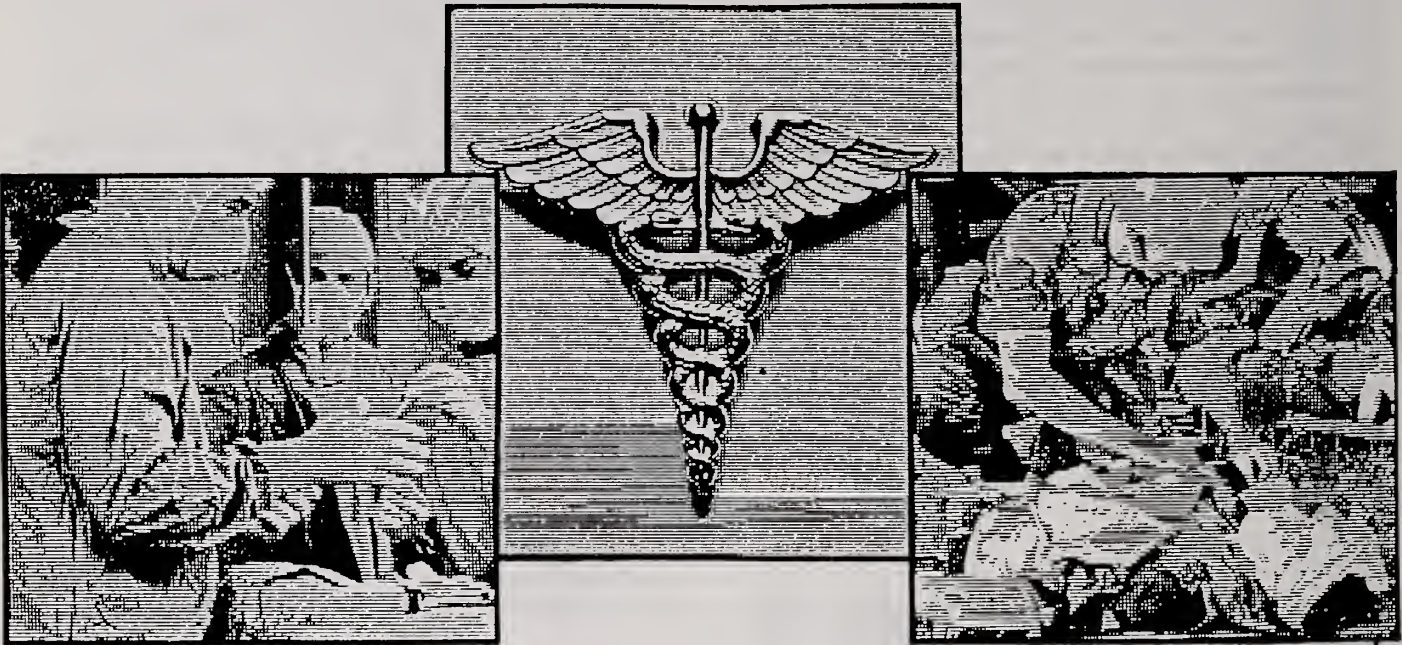
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**Resumen:** La ausencia de perfiles descriptivos de las características antropométricas y funcionales de nuestros gimnastas dificultan la evaluación objetiva de su forma deportiva y la prestación de servicios técnicos. Este estudio describió la composición corporal, somatotipo, madurez fisiológica, flexibilidad y tolerancia cardiorespiratoria de 30 atletas (femenino;  $n=12$  y masculino;  $n=18$ ) miembros de la pre-selección nacional puertorriqueña de gimnasia artística y presentó comparaciones con grupos de gimnastas reportados en la literatura. Los resultados indicaron diferencias entre los sexos en las variables: peso, suma de panículos, grasa corporal, masa corporal activa, endomorfia, mesomorfia, ISA, AMB, CMB, flexibilidad y  $VO_2\max$  ( $L\cdot\min^{-1}$ ), ( $p<.05$ ). Los resultados se encuentran dentro de la amplitud demostrada por gimnastas de alto rendimiento reportados en la literatura.

La gimnasia es una disciplina deportiva que formó parte de los Primeros Juegos Olímpicos Modernos efectuados en el 1896 en la ciudad de Atenas, Grecia.<sup>1</sup> Actualmente la gimnasia se compone de dos modalidades: la gimnasia artística o tradicional y la rítmica. La gimnasia artística para mujeres consiste de cuatro eventos: el salto del caballo, barras asimétricas, viga de equilibrio y ejercicios de piso/manos libres. Los hombres tienen seis opciones: salto del caballo, barras paralelas, barra fija, caballo con arzones, anillas y ejercicio de piso/manos libres. La modalidad rítmica es un evento exclusivo para mujeres y se compone de eventos de sogá, bola, clavos, cinta y aro. Esta modalidad fue incorporada como disciplina olímpica durante los Juegos Olímpicos de los Angeles en el 1984.<sup>2</sup>

La primera participación femenina en la gimnasia artística a nivel olímpico ocurrió en 1928 durante las olimpiadas en Amsterdam.<sup>3</sup> Las gimnastas puertorriqueñas participaron por primera vez en una competencia del ciclo olímpico en el 1975 durante los VII Juegos Panamericanos efectuados en México.<sup>4</sup> La primera participación de los gimnastas masculinos puertorriqueños en una

competencia del ciclo olímpico ocurrió en el 1974 durante los XII Juegos Centro Americanos y del Caribe efectuados en Santo Domingo, República Dominicana. En estos campeonatos un gimnasta puertorriqueño obtuvo medalla de plata.

Las características técnicas y las demandas metabólicas durante el entrenamiento y la ejecutoria competitiva de la gimnasia artística han sido motivo de estudio. Bompá<sup>5</sup> clasifica la gimnasia en el grupo de deportes que dependen del perfeccionamiento de la coordinación y forma de las destrezas. Este grupo de deportes incluye aquellos en los cuales la ejecutoria durante la competencia en la gran mayoría de las ocasiones, depende del arte de presentar con propiedad y perfección una o varias destrezas. Además, en estos deportes la actuación de atleta se juzga subjetivamente por un panel cuyos miembros, independientes entre sí, emiten su parecer utilizando un sistema de base numérico. Chávez, Lanier y Torres<sup>6</sup> han clasificado la gimnasia en base a la teoría y metodología del entrenamiento como un deporte de coordinación y arte competitivo en unión a las disciplinas de clavados, velas, tiro, nado sincronizado y equitación. De acuerdo al modelo de Chávez, Lanier y Torres, la gimnasia y todos estos deportes comparten en común: 1) la estructura del plan de entrenamiento; 2) la duración del entrenamiento necesario para la especialización; 3) el alto nivel de creatividad, glamour y acción sicomotora; 4) la incidencia y tipo de lesión durante el entrenamiento y la competencia; y 5) el tipo de servicio especializado en salud deportiva.

La tolerancia cardiorespiratoria,  $VO_2$ , la fortaleza muscular, la potencia muscular y la tolerancia local muscular son considerados factores relevantes para un buen rendimiento en la gimnasia. Mathews y Fox<sup>7</sup> en su sistema de clasificación basado en el tiempo de ejecutoria, plantean que el sistema energético predominante en la gimnasia consiste en 90% de fuentes no oxidativas y 10% de combinación no oxidativa-oxidativa. Thoden, Wilson y MacDougall<sup>8</sup> reconocen la relevancia de las fuentes energéticas no oxidativas en la ejecutoria de la gimnasia, pero argumentan que el proceso de recuperación es un proceso oxidativo y que el ritmo al cual las fuentes musculares de alta energía pueden ser reemplazadas durante la recuperación, en gran medida dependen de la máxima tolerancia cardiorespiratoria ( $VO_2\max$ ) del individuo. Dal Monte<sup>9</sup> en su sistema de clasificación de base biomecánica considera la gimnasia un deporte de destreza dependiente de gran fortaleza y potencia mus-

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cular. Además del nivel de fortaleza, potencia y tolerancia local muscular, la gimnasia requiere características antropométricas (escaso peso y talla, largo de tronco, largo de brazos) y neuromotoras (agilidad, balance, coordinación, flexibilidad) que permitan la ejecutoria de acrobacias a través de movimientos rápidos.<sup>10, 11</sup>

La literatura científica presenta escasos datos sobre los atletas puertorriqueños en general y por especialidad deportiva, ya sean estos infantiles, juveniles o adultos. El perfil antropométrico y fisiológico de los gimnastas puertorriqueños no ha sido documentado. La ausencia de perfiles descriptivos de las características antropométricas y funcionales del gimnasta puertorriqueño dificultan la evaluación objetiva de su forma deportiva y la prestación de servicios técnicos y clínicos. El propósito de este estudio fue describir indicadores de desarrollo y madurez fisiológica, composición corporal, somatotipo, flexibilidad y la tolerancia cardiorespiratoria de la pre-selección nacional puertorriqueña femenina y masculina de gimnasia artística y hacer comparaciones con grupos de gimnastas reportados en la literatura.

### Materiales y Métodos

**Sujetos.** Un grupo de 30 gimnastas (hembras n=12 y varones n=18) miembros de la pre-selección nacional puertorriqueña de gimnasia artística durante el año 1988, fueron evaluados luego de haber sido informados y obtener su consentimiento. Los datos fueron obtenidos durante una evaluación del nivel de aptitud física en la Unidad de Fisiología del Ejercicio del Centro de Salud Deportiva y Ciencias del Ejercicio del Albergue Olímpico de Puerto Rico.

### Procedimientos

**Indicadores de desarrollo y madurez fisiológica.** Las normas del Centro Nacional para Estadísticas de la Salud<sup>22</sup> fueron utilizadas para la estimación de la percentila del peso y la estatura de ambos equipos. La edad de la menarquia fue reportada por cada gimnasta femenina durante una entrevista y evaluación del estado de su salud previo a la evaluación morfofuncional.

**Composición corporal.** En los gimnastas mayores de 17 años el porcentaje de grasa fue estimado de la densidad corporal de acuerdo a la ecuación de Siri.<sup>14</sup> La densidad corporal fue estimada utilizando panículos cutáneos (triceps, suprailíaco y muslo) mediante la ecuación de Pollock, Schmidt y Jackson.<sup>15</sup> En los gimnastas menores de 17 años el porcentaje de grasa fue estimado mediante las ecuaciones de regresión de Boileau, Lohman y Slaughter<sup>16</sup> utilizando dos panículos cutáneos (triceps y subescapular). La ecuación utilizada varió de acuerdo a la edad del sujeto. La masa corporal activa (MCA) o peso libre de grasa fue calculada restando el peso graso del peso corporal. El índice de sustancia activa (ISA), el cual representa la cantidad de masa corporal activa relativa a la talla, fue calculado de acuerdo a Tittel y Wuscherk<sup>17</sup> según la siguiente ecuación:

$$ISA \text{ g.cm}^{-3} = (MCA \text{ g} \times 100) / Talla^3 \text{ cm}.$$

La **circunferencia muscular del brazo (CMB)** y el **área muscular del brazo (AMB)** fueron determinadas utilizando el espesor del panículo cutáneo del triceps (PCT) y la circunferencia del brazo (CB) de acuerdo a las

siguientes ecuaciones según descritas por Caldarone, Leglise, Giampietro y Berlutti.<sup>18</sup>

$$CMB \text{ cm} = CB - \pi PCT$$

$$AMB \text{ cm}^2 = CMB^2 / 4\pi$$

**Somatotipo.** El peso y la talla fueron determinados utilizando una balanza calibrada y un estadiómetro, respectivamente. Las medidas requeridas para la determinación del somatotipo (SOM) antropométrico de Health-Center<sup>12</sup> fueron obtenidas de acuerdo al procedimiento descrito por Carter.<sup>13</sup>

**Flexibilidad.** La flexibilidad de la parte posterior del muslo y la espalda baja fue medida utilizando la prueba "sentado y estirar" de acuerdo a los procedimientos descritos por la AAHPERD.<sup>19</sup>

**Tolerancia cardiorespiratoria.** El consumo máximo de oxígeno (VO<sub>2</sub>max) fue estimado mediante una prueba submaximal de ciclo ergometría utilizando los procedimientos descritos por Sjostrand<sup>20</sup> según modificados por la "YMCA".<sup>21</sup> La frecuencia cardíaca fue obtenida de un trazado electrocardiográfico utilizando un electrocardiograma Marquette.

**Análisis de datos.** Para cada grupo se calculó la media y la desviación estándar de cada una de las variables y cada uno de los componentes del SOM. Los procedimientos utilizados para el análisis del SOM fueron aquellos descritos por Carter.<sup>23</sup> Una prueba de t para grupos independientes fue utilizada para evaluar las diferencias entre los promedios de las variables por sexo. Los datos fueron analizados utilizando el programa computarizado "Statistical Package for the Social Sciences".<sup>24</sup> El nivel de significancia estadística fue establecido al 0.05.

### Resultados y Discusión

La tabla I contiene las características antropométricas, somatotipo, composición corporal y el nivel de flexibilidad de

TABLA I

Media y Desviación Estándar del Somatotipo, Variables Antropométricas, de Composición Corporal y Flexibilidad

Número de Sujetos	Sexo	
	Femenino 12	Masculino 18
EDAD (años)	14.7 ± 1.2	15.0 ± 3.2
PESO (kg)	46.0 ± 6.0	50.3 ± 11.5
TALLA (cm)	153.7 ± 5.9	157.5 ± 12.4
SUMA 4 panículos (mm)	41.6 ± 9.6	30.9 ± 4.8*
MCA (kg)	37.9 ± 3.7	45.5 ± 10.9*
ISA (g.cm <sup>-3</sup> )	1.041 ± 0.1	1.146 ± 0.1*
CMB (cm)	22.7 ± 1.2	27.8 ± 4.2
AMB (cm <sup>2</sup> )	41.2 ± 4.2	62.9 ± 18.2*
ENDO	3.0 ± 0.8	2.2 ± 0.4*
MESO	4.0 ± 0.5	5.2 ± 1.0*
ECTO	2.9 ± 0.6	2.8 ± 1.2
FLEXIBILIDAD (cm)/ SENTADO Y ESTIRAR	46.4 ± 3.5	38.7 ± 7.2*

MCA=masa corporal activa

ISA=índice de sustancia activa

CMB=circunferencia muscular del brazo

AMB=área muscular del brazo

\*-p<0.05



los gimnastas de ambos sexos en este estudio. Los resultados indicaron diferencias entre los sexos en las variables peso, suma de panículos, endomorfia, mesomorfia, grasa corporal, MCA, ISA, CMB, AMB, flexibilidad, y consumo máximo de oxígeno ( $L \cdot min^{-1}$ ). ( $p < .05$ ).

**Características generales e indicadores de desarrollo y madurez fisiológica.** Once del total de 12 féminas demostraron un peso menor y todas una talla menor que la percentila 50 para niñas norteamericanas de la misma edad.<sup>22</sup> El promedio de la percentila del peso y la talla fue 34.2 y 22.5, respectivamente. La edad promedio de la menarquia fue 13 años. Veinticinco por ciento de la población femenina estudiada (3 gimnastas) reportó no haber alcanzado la menarquia. La edad promedio de estas tres gimnastas, fue 13.3 años. El valor promedio de peso y talla de los varones fue más bajo que la percentila 50 de niños norteamericanos de las mismas edades.<sup>22</sup> Los varones fueron 9.5% más pesados y 2.4% más altos que las hembras.

Estudios han reportado que gimnastas femeninas de alto rendimiento (campeones mundiales y olímpicas), en su inmensa mayoría pre adolescentes y adolescentes, demuestran un peso, talla, y nivel de madurez fisiológica menor que aquellos de la población general de su misma edad y sexo.<sup>25</sup> La literatura describe a los gimnastas masculinos de alto rendimiento como adolescentes y post adolescentes.<sup>26</sup> Similar a otros grupos de gimnastas masculinos de alto nivel de destrezas, nuestros gimnastas masculinos demuestran un peso y talla menor que aquellos de la población general de su misma edad y sexo. Esto es contrario a la gran mayoría de otros deportes.<sup>27</sup> La baja estatura y peso son considerados características antropométricas que facilitan la ejecutoria de acrobacias, especialmente las asociadas con la gimnasia artística.

Previo a la pubertad, las características antropométricas de ambos sexos demuestran la tendencia a ser similares.<sup>28</sup> Hasta los diez años los sexos demuestran ser similares en el largo de las piernas, circunferencia del brazo, peso e índice ponderal. Sin embargo las características antropométricas sufren un gran cambio durante el período de la pubertad.<sup>29</sup> En los varones se observa un ensanchamiento de los hombros y en las hembras de las caderas. Estos cambios son de trascendental importancia para la ejecutoria de las diferentes destrezas requeridas por la gimnasia artística. La estrechez de los hombros en las hembras relativo a los varones, dificulta el desarrollo de fuerza en la extremidad superior.<sup>30</sup> Las caderas anchas a su vez proveen a la hembra un centro de gravedad más bajo que el varón.<sup>30</sup> Esto facilita en la hembra más que en el varón la ejecutoria de acrobacias que requieran del balance estricto del cuerpo. Tan et al<sup>11</sup> han sugerido que cada uno de los eventos en la gimnasia requiere un perfil antropométrico específico. El grupo de gimnastas Chinos estudiados por Tan et al<sup>11</sup> demostró que aquellos sobresalientes en las anillas poseían brazos anchos y cortos; en el caballo con arzones sobresalieron aquellos con brazos largos y tronco corto; en la barra horizontal aquellos con manos y brazos largos; en las paralelas los que demostraron mayor nivel de fortaleza en "apretón de manos"; y en ejercicio de piso y salto aquellos con piernas y tendón de aquiles corto.

**Composición Corporal.** La suma de 4 panículos (triceps, subescapular, supraespinal y pantorrilla medial) fue mayor en las hembras que en los varones ( $p < .05$ ). Esta diferencia fue de una magnitud de 25.7%. El equipo olímpico femenino de Brasil<sup>31</sup> (12.2 años), la selección nacional venezolana<sup>32</sup> (13.0 años) y la selección nacional dominicana<sup>33</sup> (14.8 años) de gimnasia artística han demostrado una amplitud de 15 a 25mm en la suma de los panículos del triceps, subescapular y supraespinal. Carter y Yuhasz<sup>34</sup> han demostrado que los panículos de los gimnastas olímpicos son de menor espesor que el de atletas de otros deportes, exceptuando el de saltadores y corredores de pista.

El porcentaje de la grasa corporal de las hembras fue mayor que el de los varones ( $p < .05$ ). La magnitud de la diferencia fue 43%. Wilmore<sup>35</sup> reportó una amplitud de 9 a 24% de contenido de grasa corporal en gimnastas femeninas infantiles y juveniles. La amplitud del valor de grasa corporal demostrado por gimnastas de la modalidad artística de 13-15 años no ganadores de medallas durante el Campeonato Juvenil Europeo de 1984 fue de 13.8% a 19.9%.<sup>18</sup> La literatura presenta escasos datos sobre el contenido de grasa corporal de gimnastas masculinos infantiles y juveniles de alto nivel de destrezas. Comparado con atletas de otros deportes el gimnasta masculino de alto rendimiento demuestra un bajo contenido de grasa corporal y un alto contenido de MCA. Wilmore<sup>35</sup> ha reportado que el valor promedio de grasa corporal para gimnastas masculinos infantiles y juveniles es 5%. El grupo Europeo masculino estudiado por Calderone et al<sup>36</sup> demostró valores de grasa corporal entre 4.9 y 9.0%.

La MCA, CMB, y AMB de los varones fue mayor que la determinada para las hembras ( $p < .05$ ). La diferencia en estas consistió en 16.7%, 18.4% y 34% para la MCA, CMB y AMB, respectivamente. Gimnastas femeninas europeas de 13 a 15 años estudiadas por Calderone et al<sup>18</sup> han demostrado una amplitud para la MCA e ISA de 30.43 a 38.19 kg y 0.938 a 1.028 g/cm<sup>3</sup>, respectivamente. Las gimnastas juveniles europeas, <12 años y 13-15 años, han demostrado valores promedio para la CMB de 20 y 21 cm, respectivamente. En el AMB este mismo grupo demostró un promedio de 33 y 37cm<sup>2</sup>, respectivamente. El grupo europeo masculino demostró un AMB promedio de 24 cm para los varones de 15 años y 29 cm para >15 años. La CMB promedio para el grupo de varones europeos de 15 años 48.6 cm<sup>2</sup> y para los de 16 a 18 años 70 cm<sup>2</sup>. Comparado con atletas de otros deportes el gimnasta masculino de alto rendimiento demuestra un bajo contenido de grasa corporal y un alto contenido de MCA.

Los cambios hormonales asociados con la pubertad afectan la composición corporal de ambos sexos. Durante este período las hembras demuestran un aumento en la acumulación de tejido adiposo y los varones de MCA.<sup>28, 29</sup> Esta diferencia en la composición corporal, mayor cantidad de tejido adiposo en la hembra y de MCA en el varón, se mantiene aun en atletas que participan en deportes de un alto expendio energético. La mayor cantidad de grasa corporal en la mujer le provee desventaja en deportes en los cuales se requiere que esta levante o mueva su peso en contra de la gravedad. Esto es

debido a que la hembra tiene que mover una mayor cantidad de grasa corporal con una menor cantidad de masa corporal que el varón.

**Somatotipo.** La ilustración 1 presenta un somatograma con la localización del somatotipo promedio del grupo femenino y masculino. El promedio del somatotipo (endomorfa-mesomorfa-ectomorfa) del grupo femenino fue 3.0-4.0-2.9 y el del grupo masculino fue de 2.2-5.2-2.8. La media de estos somatotipos se encuentra en el sector del somatograma correspondiente a mesomorfo balanceado y ectomorfo mesomorfo para los grupos de hembras y varones, respectivamente.

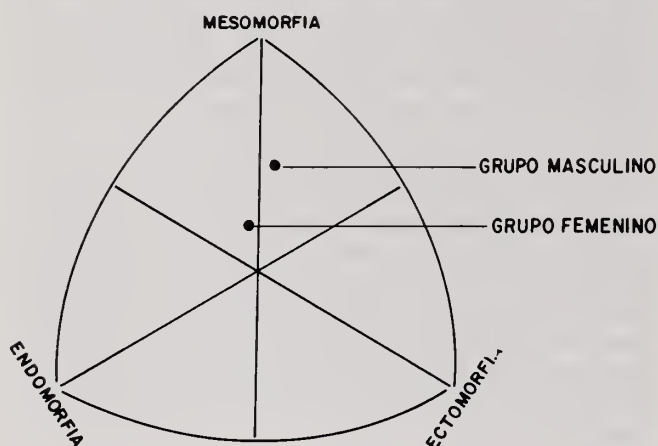


Ilustración 1. Somatograma de somatotipos medios de gimnastas puertorriqueños.

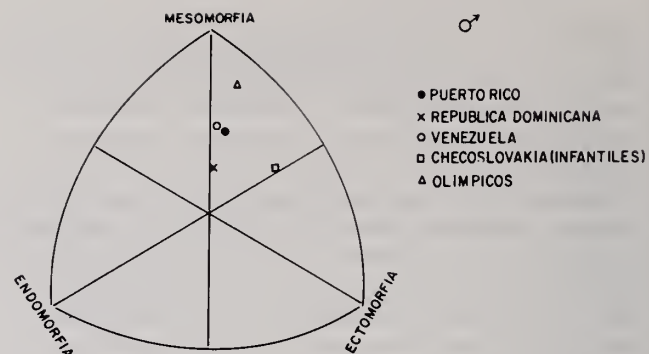


Ilustración 3. Somatograma de somatotipos medios de grupos de gimnastas masculinos. Puerto Rico (datos presentes), República Dominicana (33), Venezuela (32), Checoslovacos (37) y Olímpicos (50).

El somatotipo promedio de varios grupos de gimnastas femeninos y masculinos reportados en la literatura se presentan en la ilustración 2 y 3 respectivamente. Las gimnastas féminas de alto rendimiento que presenta la literatura<sup>37</sup> demuestran ser pre adolescentes y adolescentes, y sus somatotipos se encuentran alrededor del valor 2-4-3.5. (1.8-3.3-4.1 Brasil,<sup>31</sup> 2.3-3.3-2.7 República Dominicana,<sup>33</sup> 2.2-4.4-3.0 Venezuela<sup>32</sup>). Carter<sup>38</sup> ha reportado que los grupos de gimnastas femeninas presentan poca variabilidad en endomorfa y mayor variabilidad en mesomorfa y ectomorfa. Además, ha identificado que mientras mayor la edad de la gimnasta mayor tiende a ser su endomorfa. Carter también ha demostrado que los gimnastas masculinos olímpicos demuestran dominancia del componente somatotípico mesomórfico. Grupos de gimnastas masculinos infantiles y juveniles han demostrado los siguientes somatotipos: Checoslovacos de 12 años 1.5-4.4-3.9<sup>37</sup> y la selección nacional venezolana (edad media 17.2 años) 1.7-5.4-2.5.<sup>32</sup> Los gimnastas masculinos de la República Dominicana han demostrado un SOM de 1.8-3.7-2.5.<sup>33</sup> Baily y Mirwald<sup>39</sup> revisaron la literatura relacionada con los efectos del entrenamiento deportivo en el crecimiento y desarrollo del niño. Estos señalaron que el rendimiento físico en destrezas motoras esta positivamente relacionado con la mesomorfa y negativamente con la endomorfa. Un alto nivel de MCA en unión a un alto componente mesomórfico son típicos de deportes que requieren un alto grado de fuerza y potencia.

**Flexibilidad.** El grupo femenino demostró un mayor grado (16.6%) de flexibilidad de la parte posterior del muslo/espalda baja que el masculino ( $p < .05$ ). Haywood, Clark y Mayhew<sup>40</sup> han reportado que gimnastas femeninas norteamericanas de 7 a 12 años de edad demuestran un valor promedio de  $61.3 \pm 4.5$  cm para la flexibilidad de la parte posterior del muslo y espalda baja. La percentila 99 para la población general de hembras norteamericanas de 13 a 15 años es 49 cm.<sup>19</sup> La información relacionada con los niveles de flexibilidad de varones gimnastas es muy escasa. La percentila 99 para la población general de varones norteamericanos de 13 a 15 años es 44 cm y para los mayores de 15 años es 48 cm.<sup>19</sup>

La variable flexibilidad demuestra diferencias asociadas al sexo.<sup>28</sup> A partir de los 10 años la hembra demuestra un

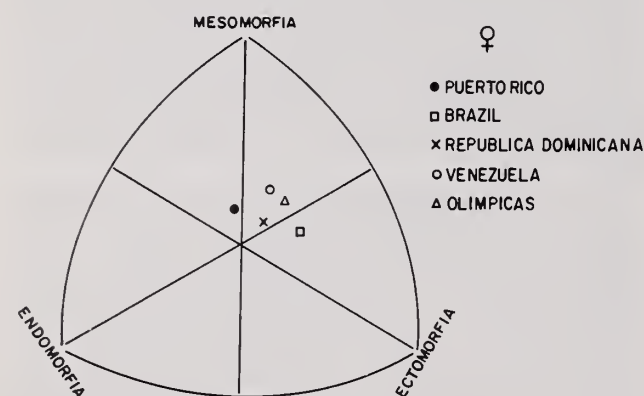


Ilustración 2. Somatograma de somatotipos medios de grupos de gimnastas femeninas. Puerto Rico (datos presentes), Brazil (31), República Dominicana (33), Venezuela (32), y Olímpicas (50).



gradual aumento en los niveles de flexibilidad que continúa hasta los 16 años.<sup>28</sup> En el varón el aumento en los niveles de flexibilidad se nota a partir de los 14 años y continúa su aumento hasta los 17 años.<sup>28</sup> Contrario a otras variables fisiológicas y de aptitud física los niveles de flexibilidad son mayores en la hembra que en el varón. La diferencia entre sexos en la prueba de sentado y estirar fluctúa entre 2.5 cm y 7.6 cm.<sup>28</sup> En este estudio la diferencia entre sexos fue 7.7 cm.

**Tolerancia cardiorespiratoria.** La tabla 2 presenta la predicción obtenida del  $\dot{V}O_2\text{max}$ . Ambos grupos demostraron poseer un alto nivel de tolerancia cardiorespiratoria. El grupo masculino demostró un  $\dot{V}O_2\text{ max}$  absoluto ( $\text{L min}^{-1}$ ) 20% mayor al del grupo femenino,  $p < .05$ . Sin embargo, cuando el peso de los gimnastas fue tomado en consideración, el  $\dot{V}O_2\text{max}$  del grupo masculino fue similar al del femenino ( $p = .05$ ). Grupos de gimnastas femeninos de diferentes niveles de destrezas han demostrado los siguientes valores de  $\dot{V}O_2\text{max}$ : 36.3  $\text{ml/kg.min}^{-1}$  norte americanas universitarias,<sup>41</sup> 45.2  $\text{ml/kg.min}^{-1}$  norte americanas estudiantes de escuela superior<sup>42</sup> y 42.5  $\text{ml/kg.min}^{-1}$  jóvenes europeas.<sup>43</sup> La literatura demuestra que el  $\dot{V}O_2\text{max}$  absoluto del sexo femenino aumenta con la edad hasta aproximadamente los 14 años cuando se estabiliza, mientras que el  $\dot{V}O_2\text{max}$  relativo al peso disminuye con la edad.<sup>44</sup> La disminución relacionada a la edad ha sido asociada con el aumento en grasa corporal que demuestra la mujer con su desarrollo fisiológico.<sup>45</sup>

TABLA II

## Media y Desviación Estándar de la Potencia Aeróbica

Número de Sujetos	Sexo	
	Femenino 12	Masculino 18
$\dot{V}O_2\text{ max. (L.min}^{-1}\text{)}$	$2.4 \pm 0.5$	$3.0 \pm 0.6^*$
$\dot{V}O_2\text{ max. (ml/kg.min}^{-1}\text{)}$	$52.7 \pm 8.6$	$58.5 \pm 7.3$
$\dot{V}O_2\text{ max. (ml/kgMCA. min}^{-1}\text{)}$	$63.7 \pm 9.7$	$68.4 \pm 13.4$
Potencia Max. ( $\text{kgm. min}^{-1}\text{)}$	$1033.3 \pm 200$	$1287.3 \pm 281^*$

\*= $P < 0.05$

Según Wilmore<sup>46</sup> gimnastas masculinos de alto rendimiento (20 años, 178.5 cm y 62.9 kg) han demostrado un valor promedio de  $\dot{V}O_2\text{max}$  de 55.5  $\text{ml/kg min}^{-1}$ . Bar-Or<sup>47</sup> ha descrito que el  $\dot{V}O_2\text{max}$  ( $\text{L min}^{-1}$ ) del sexo masculino aumenta con la edad hasta aproximadamente los 18 años cuando se observa una estabilización. Una vez el  $\dot{V}O_2\text{max}$  es ajustado al peso corporal los jóvenes demuestran un aumento muy leve. Se ha sugerido que para controlar los efectos del crecimiento/desarrollo se tome en consideración las dimensiones físicas del individuo y el  $\dot{V}O_2\text{max}$  sea expresado relativo a la talla<sup>2</sup> y talla<sup>3</sup>, en adición al peso y MCA.<sup>48</sup> Este concepto de dimensionalidad aplicado a la tolerancia cardiorespiratoria es un área de controversia muy particular al área de comparaciones relacionadas al proceso de crecimiento y desarrollo.<sup>49</sup>

## Conclusión

Grupos de gimnastas de edad, sexo, y nivel de destrezas similares a los nuestros han sido estudiados desde varias perspectivas.<sup>46, 50, 51, 52</sup> Nuestros resultados se encuentran dentro de la amplitud demostrada por varios de estos estudios. La literatura demuestra que las diferencias encontradas entre los sexos pueden ser debido a factores tales como la edad, intensidad y volumen del entrenamiento, dieta, efectos genéticos, nivel de madurez fisiológica y otros factores biosociales.

La gimnasia contrario a la gran mayoría de las disciplinas deportivas reúne competidores de alto rendimiento pre adolescentes y adolescentes. El período comprendido por la pre adolescencia y la adolescencia es caracterizado por cambios acentuados en la forma, estructura, composición y función de los diferentes sistemas del organismo humano. El ritmo al cual estos cambios ocurren, dificultan el estudio de las variables cinantropométricas entre individuos y poblaciones. Carter<sup>37</sup> en sus estudios de la morfología de atletas de diferentes sexos, edades y nivel de rendimiento ha planteado que las comparaciones entre grupos de gimnastas se dificultan mucho más aún cuando desconocemos el nivel de competencia, la cantidad y calidad del entrenamiento, y la calidad de la asesoría técnico táctica de los gimnastas estudiados en la literatura.

En conclusión, estos datos descriptivos sobre el somatotipo, composición corporal, flexibilidad, nivel de madurez fisiológica y función cardiorespiratoria de los gimnastas puertorriqueños es información nueva que puede ser utilizada para: la selección de talento a temprana edad, la evaluación y entrenamiento de estos atletas, comparación con otros países y poblaciones de atletas, la prevención de lesiones, propósitos clínicos, educativos y nuevas investigaciones.

**Abstract:** This study described the body composition, somatotype, physiological maturity, flexibility and cardiorespiratory endurance of 30 gymnasts (feminine;  $n=12$  and masculine;  $n=18$ ) pre selected for the puertorrican national team and compared the results with those reported in the literature. There were significant differences between the sexes in body fat, lean body mass, ISA, CMB, AMB, endomorphy, mesomorphy, sum of skinfolds, flexibility and  $\dot{V}O_2\text{max}$  ( $\text{L.min}^{-1}$ ), ( $p < .05$ ). The results are within the range reported in the literature for elite gymnasts.

## Reconocimiento

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## Los Adolescentes y la Salud Escolar de los Años Noventa

Luisa E. Burgos, MD

**Resumen:** Son numerosos los problemas que confrontan los adolescentes al asomo de los años noventa. Tienen su base en la inversión de valores; pobres hábitos nutricionales y de higiene; inestabilidad mental, emocional y social; una deficiente educación en salud, tanto de padres como de hijos y una inexistente integración entre las diversas agencias públicas y privadas responsables de desarrollar un equipo multidisciplinario que dé soluciones a los problemas en las diferentes fases.

La Ley 70 de 1989 exige educación y actividades de prevención en todas las escuelas desde nivel elemental hasta la escuela superior como parte del currículo regular.

Urge una coordinación entre los distintos proveedores de servicios desde la etapa del diseño de planificación, implantación, divulgación y evaluación.

Este artículo pretende reunir hallazgos de diversas fuentes de estudio y las recomendaciones inminentes para la toma de acción.

Urge reunir funcionalmente al equipo de salud, la escuela, la policía, los servicios sociales y toda la sociedad en un esfuerzo conjunto, para resolver los problemas de los jóvenes adolescentes, responsables del Puerto Rico del Siglo 21. Se hace necesario el apoyo a éstos por una política y leyes que agilicen las acciones necesarias a tomar ante el reto tan difícil que presentan los críticos problemas que se confrontan en esta década. El deterioro de valores morales y la falta de educación claman por unas estrategias vitales tomadas desde la infancia y la formación de los padres así como a los distintos niveles de nuestra sociedad.

Se encuentran directamente afectados 541,450 adolescentes (12-19 años) y son el 17.4% de la población de Puerto Rico. El 10.5% de estos jóvenes son desertores escolares.

Existen entre 100,000 a 150,000 adictos a drogas y siete de cada diez comienzan a usar drogas antes de los 19 años.

La comunidad y las drogas están seriamente asociados. Los adolescentes drogadictos cometen actos delictivos y

son utilizados por adultos irresponsables que los inducen. Hay 70,000 crímenes tipo I asociados a drogas. El 85% de los confinados han estado en drogas.

Los accidentes automovilísticos por conducir en estado de embriaguez son la primera causa de muerte entre los adolescentes. Puerto Rico es el tercer país en consumo del alcohol en el mundo. El Síndrome de Inmunodeficiencia Adquirida (SIDA) y otras enfermedades sexualmente transmitidas han ido en aumento.

El 26.5% de los nacimientos anuales son de hijos de madres adolescentes. La madre adolescente tiende a tener familia numerosa y menos espaciada. La mayoría de los hijos nacen fuera del matrimonio. Por una preparación incompleta o inadecuada tienen menos oportunidades de empleo. Alrededor de un 85% no trabajan y viven de las ayudas que les ofrece el gobierno. Los matrimonios tienden a fracasar entre otros factores por la falta de preparación para afrontar las responsabilidades del matrimonio. Muchas madres solteras tienen que afrontar solas la crianza de sus hijos, ya que los padres suelen no asumir la responsabilidad de la paternidad. Comentarios, críticas y sentimientos de rechazo, culpa, aislamiento, frustración, rebeldía, inseguridad y ansiedad traen otros problemas tales como: madre afectada en su propio desarrollo físico, emocional, social y psicológico no completado aún; hijo afectado por complicaciones en el feto: asfixia por pobre intercambio de gases en el pulmón, prematuridad, anemia, infante de bajo peso, hijo de madre adicta a drogas, susceptible a infecciones (pulmonía, diarreas), deficiencias nutricionales, defectos congénitos, retardación mental. La madre adolescente presenta una alta incidencia en abortos, hemorragias, infecciones, perforación de útero que puede estar acompañado por hemorragias y daño al intestino y la vejiga, infertilidad y muerte.

Este embarazo aumenta la probabilidad de eclampsia incluyendo intensos dolores de cabeza y convulsiones; desproporción cefalopélvicas que traen las complicaciones de parto prolongado y cesáreas; distocia uterina, rotura prematura de membranas, sangría e infecciones.

De 125,000 a 150,000 niños y adolescentes padecen en Puerto Rico de enfermedad mental severa.

Otros problemas comunes en la familia de padres adolescentes son trato cruel y abuso físico y sexual a niños.

El enfoque de la nueva ley de Salud Escolar, Ley 70 del Senado de agosto de 1989 es a exigir la educación en salud en todas las escuelas elementales, intermedias y superiores como parte del currículo regular. Exige que se desarrolle el proceso de aprendizaje necesario para orientar a padres e hijos sobre: el desarrollo de valores, buenos hábitos alimenticios e higiene oral, acondicionamiento del cuerpo mediante el ejercicio físico, prevención de accidentes, no fumar, control del uso de drogas y bebidas alcohólicas, toma de decisiones para reducir los riesgos relacionados con la inestabilidad mental y emocional, aprecio del cuerpo humano dirigido a crear una actitud positiva hacia la conducta sexual, estar alertas ante señales de enfermedades y respetar los derechos de las demás personas.

La Ley insta a establecer un equipo multidisciplinario para llegar a todos los niveles del sistema de educación.

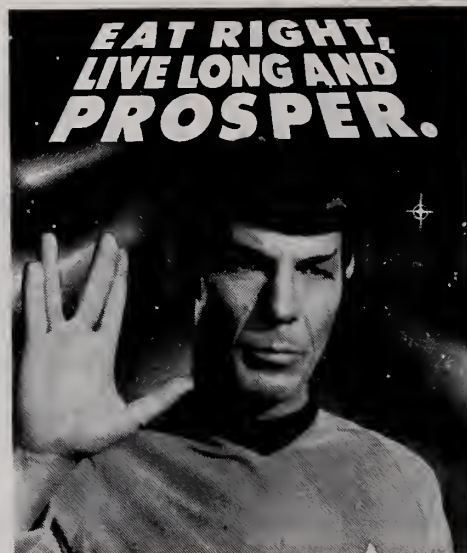
La Ley 70 establece que el Departamento de Instrucción Pública podrá recibir transferencia de recursos, personal y asesoramiento de cualquier dependencia gubernamental o privada para implantar este programa de educación en salud.

El 89.5% de los adolescentes se encuentran en las escuelas. He aquí un lugar donde las estrategias para mejorar la calidad de vida se puede lograr con un desarrollo y fortalecimiento del programa de salud escolar.

El 10.5% (56,852 adolescentes) que se encuentran fuera de la escuela requiere de otras estrategias, aunque uno de sus principales objetivos es el retorno del adolescente a la escuela.

El Programa de Salud Escolar necesita poder ejercer funciones tales como:

1. Identificar y clasificar la población meta para intervenirla efectiva y eficientemente.
2. Identificar factores de riesgo que afectan la salud física, mental y social para intervenir de inmediato en la solución de problemas.
3. Coordinar los servicios a través de vínculos estrictos de cooperación entre los distintos proveedores de servicios gubernamentales y privados desde la etapa del diseño de planificación, implantación, divulgación y evaluación.
4. Patrocinar una campaña de saneamiento del ambiente a que está expuesta la familia, promoviendo valores, actividades de familia, de comunidad y todas las actividades culturales, deportivas, religiosas, históricas y de buena salud física, mental y espiritual.
5. Promover estilos de vida saludables elevando la autoestima, promoviendo el liderazgo, la participación de pares, la comunicación efectiva, procurando una buena nutrición, ejercicios y controlando los vicios a través de la prevención y la acción directa sobre la deserción escolar, las drogas, el alcohol, el tabaquismo y la conducta sexual irresponsable.



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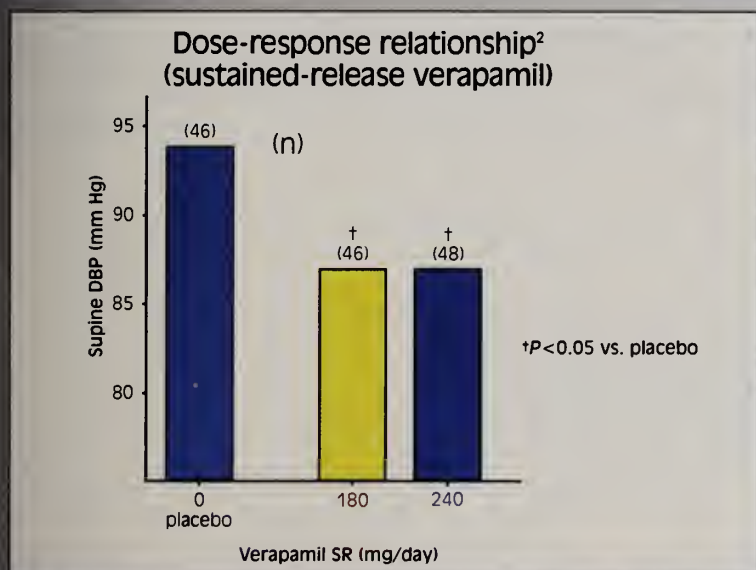
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### BRIEF SUMMARY

**Contraindications:** Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

**Warnings:** Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

**Precautions:** Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration.

Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

**Adverse Reactions:** Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°, 2°, 3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, increased urination, spotty menstruation, impotence.

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- Data on file, G.D. Searle & Co.

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# Case Presentation

## Pseudomyxoma Peritonei: Case Report and Review of the Literature

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**Summary:** Pseudomyxoma peritonei is a rare entity manifested by implants of a mucinous gelatinous material arising from either the appendix or ovary and involves the peritoneal cavity, peritoneum and omentum. Preoperative diagnosis is feasible by means of radiographic studies. The main step in the treatment is debulking surgery with appendectomy, bilateral oophorectomy and omentectomy. Adjuvant radiotherapy and chemotherapy has been used. Long term survival is around 54% at five years.

Here we present a case of a ruptured mucocoele of the appendix and pseudomyxoma who presents as massive increase in the abdominal girth of two years evolution.

Pseudomyxoma peritonei is a rare entity characterized by multiple peritoneal implants of a mucinous material that arises from either appendiceal or ovarian lesions. It was first described by Weith in 1884 and, thereafter, sporadic case reports have been published.<sup>1, 2, 3</sup>

It is our purpose to present another case and to review the etiology, presentation and management of this fascinating entity.

### Case History

This is the case of a 74 years old man without history of chronic or systemic illness admitted to our hospital on August 6, 1987 with a history of progressive increase in the abdominal girth for the last two years, that lately was associated to loss of appetite and 25 pounds weight loss.

He referred weakness, fatigue and shortness of breath of 2-3 months evolution. He also stated leg edema manifested for the first time 2-3 months prior to the evaluation.

The patient denied history of alcohol abuse, previous blood transfusions, history of hepatitis or history of river bathing.

He denied history of jaundice, abdominal pain, nausea, vomiting, constipation or diarrhea. There was no history of melena or hematochezia.

The patient also denied history of abdominal trauma or previous abdominal surgery.

Physical exam upon admission revealed a thin man with huge abdominal distention. The sclerae were anicteric. There was no parotid enlargement or spider angiomas. The lungs were clear with poor diaphragmatic excursion. There were no heart murmurs. The abdomen was huge, tense with prominent collateral circulation. A small umbilical hernia was present. The peristalsis was adequate. At epigastrium a hard mass effect was felt. No evidence of splenomegaly. The rectal exam failed to disclose masses, the prostate was rubbery and the guaiac test was slightly positive.

The laboratory evaluation revealed a WBC count of 9,100 Hgb 10.9 gm/dl and Hct of 33.6% with normochromic normocytic indexes. The platelet count was 362,000. The serum Na was 138 meq/Lt, K was 4.0 meq/Lt, Cl 99 meq/Lt, CO<sub>2</sub> 28 meq/Lt. The total bilirubin, SGOT, SGPT amylase and lipase were normal. The alkaline phosphatase was 168 u/L (NV=30-115). The total protein was 7.9 gm/dl and the albumin 3.4 gm/dl. The prothrombin time and partial thromboplastin time were normal. The urine analysis was also normal. The chest X-ray was normal except for marked decrease in lung volume due to elevation of both hemidiaphragms.

A diagnostic and therapeutic abdominal tap was done. A liter of a jelly-like substance was obtained with difficulty.

An abdominal sonogram showed a low echogenic material with multiple septations within the abdominal cavity. The liver, spleen and bowel were all displaced by this material. (Figure 1)

The abdominal CT revealed that the abdomen was almost completely replaced by a low attenuation mass which was septated containing some areas of calcification within the septae. Also marked scalloping of the liver surface was present (Figure 2)

A diagnosis of pseudomyxoma peritonei was done. The patient underwent an exploratory laparotomy in September 1987. Sixteen<sup>16</sup> liters of mucinous material were evacuated. A perforated appendiceal lesion was

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Figure 1. Transverse ultrasound. Multiloculated cystic masses with thick septations (arrowheads) and internal low level echoes. Bowel loops (black arrow) are displaced posteriorly and medially by the masses.

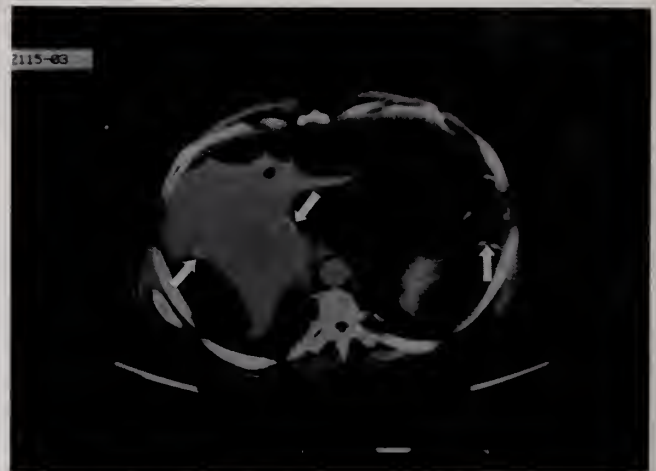
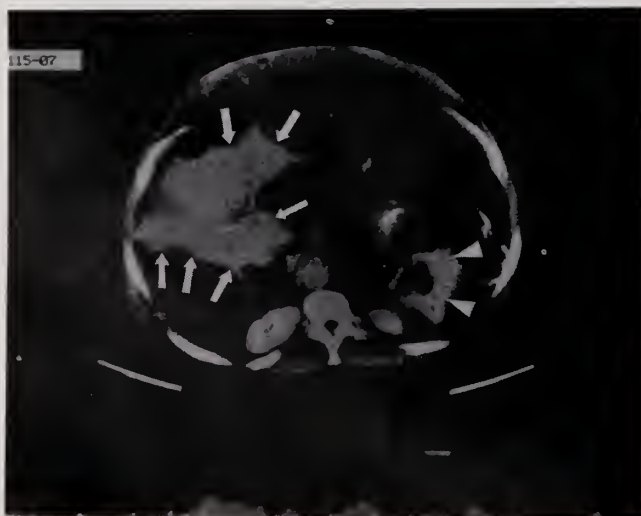
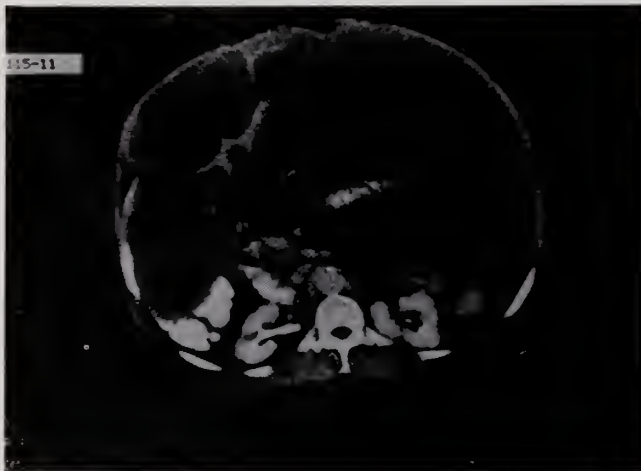


Figure 2. Transverse CT Scan. A. Multiple low attenuation masses, surrounded by discrete thick walls. Contrast filled bowel loops are displaced posteriorly failing to float up anteriorly as would be expected for ascites. The appendix could not be identified. B. Extensive scalloping of the liver (small arrows) and spleen (arrow heads) surface by the extrinsic pressure of the gelatinous masses. C. The walls of the masses contained calcifications (large arrows).

observed, so appendectomy was done. Also debulking of the mucinous implants to peritoneum, mesentery, omentum and surface of organs was performed.

The pathologic diagnosis was of pseudomyxoma peritonei due to ruptured mucocele of the appendix (Figure 3).

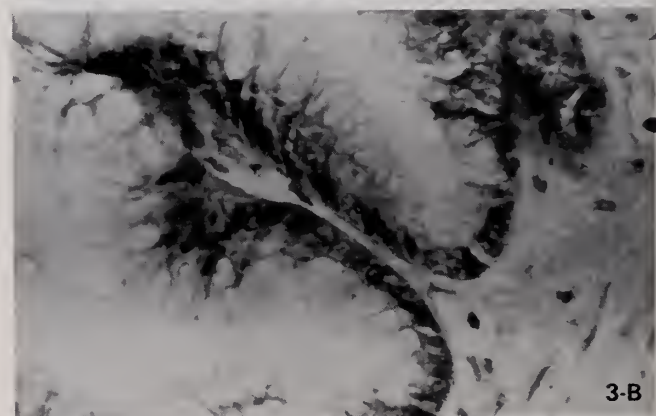
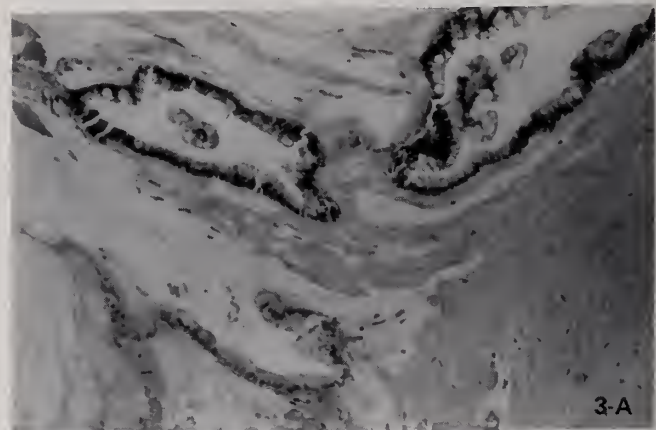


Figure 3. Mucocele of the appendix. A. Wall of the appendix invaded by neoplastic glands of colonic type. Abundant extraglandular mucin is present. B. Mild atypia of neoplastic glandular epithelium; basal placed nuclei and cytoplasm distended with mucin.



Follow-up CT Scans of the abdomen and pelvis (Figure 4) done two and ten months after surgery showed marked decrease in the size of the low attenuation masses but still there were multiple lesions infiltrating the spleen and liver, nevertheless, on follow up visits the patient referred feeling fine, having good appetite without further weight loss. His weight immediately after surgery was 126 pounds, being his actual weight 159 pounds. He denied further increase in the abdominal girth. On physical exam the abdomen was soft and depressible without evidence of distention, visceromegaly or masses.

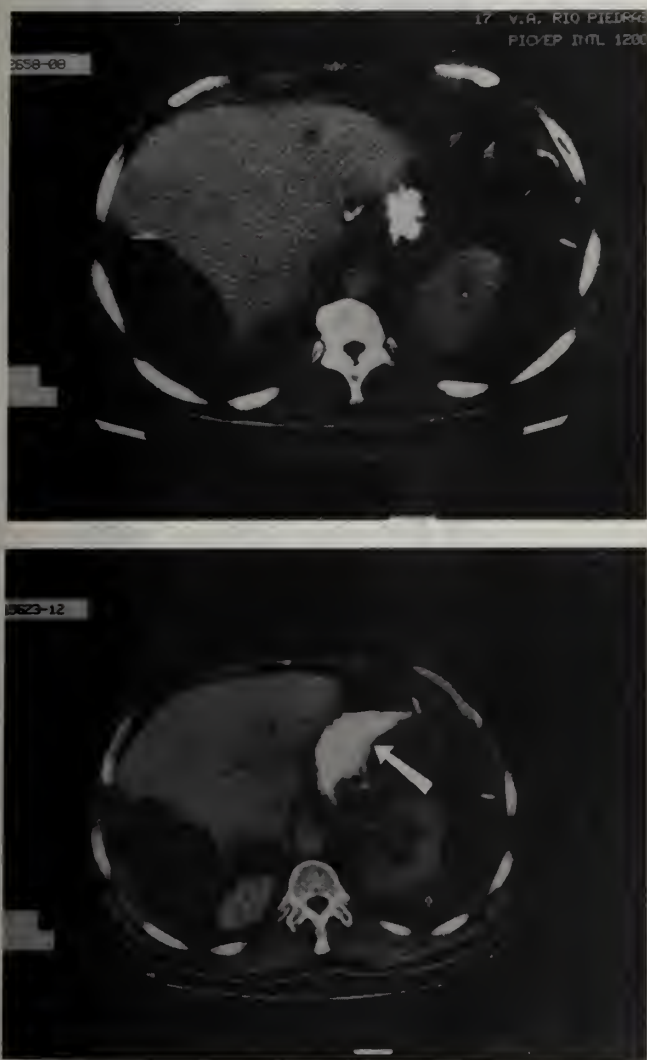


Figure 4. A. CT Scan two (2) months after surgery. Decrease in size and number of the masses with less scalloping of the liver. B. CT Scan ten (10) months after surgery. The low attenuation masses are seen displacing the stomach medially (curved arrow).

### Discussion

Pseudomyxoma peritonei is a rare entity in which the peritoneum and omentum are involved by implants of a mucinous gelatinous material that are often massive. The primary site of origin of this material rise from mucin producing lesions mainly of the ovary and appendix.

Mucocele of the appendix, defined as an abnormal mucous accumulation distending the appendiceal lumen was first described by Rokitsansky in 1842, thereafter, have been controversy about the pathology of this condition. Two theories have been proposed. The obstructive theory states that as a result of proximal appendiceal obstruction the appendix is stimulated to produce an excessive amount of mucin.<sup>4</sup> The second postulates that as a consequence of obstruction the appendiceal mucosa undergoes a malignant transformation leading to the formation of the mucocele.<sup>5</sup> Woodruff named this malignant transformation as adenocarcinoma grade 1.

The later development of pseudomyxoma peritonei in these patients also has been controversial. The original description done by Weith in 1884 ascribed the development of pseudomyxoma peritonei to peritoneal irritation produced by the spillage of mucin from a ruptured mucocele, with the resulting metaplasia of the peritoneal cells. Others now visualize the development of this entity to metastatic peritoneal implants of low grade malignant cells.<sup>5</sup> Nevertheless, Berry was able to produce a condition similar to pseudomyxoma peritonei in rabbits simply by ligation of the appendix with an open distal stump.<sup>6</sup>

Mucocele of the appendix are found in around 0.2% of appendectomies.<sup>7</sup> Around 25-50% of all mucoceles are incidental findings at surgery. The clinical presentations of symptomatic patients are varied from vague abdominal pain to a palpable mass in up to 50% of the patients.<sup>8</sup> Intussusception of the mucocele is not an uncommon presentation, twenty-seven<sup>27</sup> cases have been reported.<sup>9, 10</sup>

In 1936, Akerlund<sup>11</sup> described preoperative radiographic diagnosis of mucocele. While the barium enema has long been the diagnostic tool used, sonogram and CT scan have shown to be valuable in the diagnosis of mucocele and pseudomyxoma peritonei.

Recent reports have described several CT findings in pseudomyxoma, as is the presence of septated collections of fluid throughout the abdomen and pelvis.<sup>12, 13</sup> Some considered scalloping of the liver due to extrinsic pressure deformities on the liver surface by adjacent peritoneal tumor implants as suggestive of pseudomyxoma peritonei.<sup>14-16</sup>

When an unruptured mucocele is diagnosed, the accepted treatment is simple appendectomy. Nevertheless, when it is ruptured and pseudomyxoma has ensued the therapy is controversial.

Fernández<sup>17</sup> reviewed 38 cases of pseudomyxoma peritonei that were treated at the M.D. Anderson Hospital, where different treatment strategies provided a 54% survival at five<sup>5</sup> years and a 18% survival at ten<sup>10</sup> years.

The main step in the treatment of this condition is the initial surgery that should consist of omentectomy, appendectomy, and in the female, bilateral oophorectomy and removal of all possible peritoneal implants.<sup>18</sup>

Adjunctive therapy have consisted of either radiotherapy, chemotherapy or a combination of both. Most common chemotherapeutic agents used are melphalan and fluorouracil. Radiotherapy has usually been used after second look operations have shown persistent disease. Some reports conferred a longer survival with radiotherapy.<sup>17</sup>

Death in those patients with pseudomyxoma are because of extensive peritoneal disease with loss of intestinal function and obstruction, not as a result of visceral invasion.

**Resumen:** Pseudomyxoma peritonei es una condición rara que se manifiesta por múltiples implantes de un material gelatinoso en la cavidad abdominal, omento y peritoneo. Usualmente surge de lesiones de la apéndice o del ovario. El diagnóstico se puede sospechar preoperatoriamente basándose en estudios radiográficos. El tratamiento básico de esta condición lo es cirugía donde debe extraerse la apéndice y los ovarios al igual que el omento. Debe sacarse todo aquel implante que sea posible. Se ha utilizado quimioterapia y radioterapia para ayudar a mejorar la sobrevida a cinco (5) años, la cual se ha reportado es alrededor de 54%.<sup>6</sup> Aquí presentamos un caso de un paciente con mucocoele de la apéndice y pseudomyxoma peritonei que se presenta con una distensión masiva de su abdomen de dos años de evolución.

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# Spontaneous Pneumomediastinum

José Ramírez-Rivera, MD, FACP, FCCP

**Abstract:** A 15-year-old pregnant girl developed severe substernal apain during the final effort to give birth to her first child. Shortly thereafter a growing crepitant suprasternal swelling was noted. Pneumomediastinum and subcutaneous emphysema was clearly demonstrated by a chest film showing mediastinal air dissecting towards the neck and supradiaphragmatically. The causes and physiopathology of spontaneous pneumomediastinum are reviewed. The therapeutic use of oxygen is discussed.

Spontaneous pneumomediastinum has various causes and diverse presentations. Although known in Europe for more than a century,<sup>1</sup> most cases have been identified after the detailed account by Hamman in 1939.<sup>2</sup> Pneumomediastinum is readily associated with trauma to the neck and thorax and with mechanical ventilation. When it occurs spontaneously, however, it may become a problem in the differential diagnosis of throat and chest pain.<sup>3-5</sup> This report describes the development of pneumomediastinum in a healthy young girl who developed ches pain while bearing down in the final effort to give birth to her first child.

## Case Report

A 15-year-old girl was admitted at term to a regional hospital to deliver her first pregnancy. She was healthy. She had not had a recent respiratory illness and she denied wheezing or recurrent respiratory infections. Active labor began shortly after admission and, fourteen hours later, when she gave the final "push" that propelled out the head of her child, she experienced a bursting sensation in the upper substernal area which radiated to both sides of the neck. The pain was soon followed by a suprasternal and lower cervical compressible and crepitant swelling, which began to grow in size. At no time did she feel short of breath or have difficulty swallowing. A chest film obtained six hours after delivery showed air outlining the heart shadow and the mediastinal vascular structures and air in the subcutaneous tissue of the neck. Because the tender subcutaneous mass grew, extending towards the face, the patients was transferred to the University Hospital for further evaluation and treatment.

On admission, there was a crepitant swelling extending between the angle of the jaw and a level 3 cm below both clavicles. A second roentgenogram, twenty-five hours after delivery, showed air in the mediastinum and the supraclavicular areas. The left hemidiaphragm was now exquisitely outlined by an extrapleural thin layer of air (Figure 1). Seven hours later, after reassuring the patient

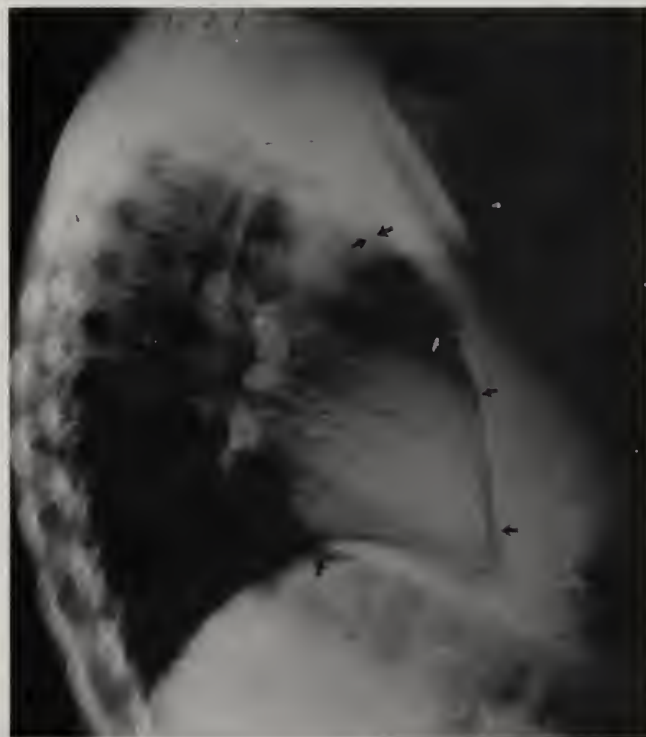
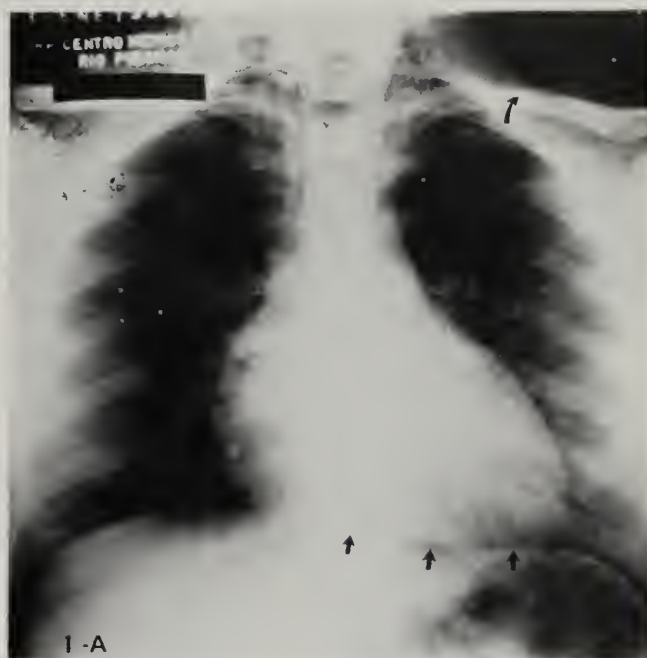


Figure 1. Chest roentgenogram dated January 3. A. P A view showing air in the supraclavicular areas. The mediastinal structures and the left hemidiaphragm are distinctly delineated by air. B. lateral view showing retrosternal air extending in streaks towards the neck. A thin collection of air beneath the parietal pleura outlines completely the left hemidiaphragm.

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and stressing the importance of the continuous use of oxygen, treatment with 50 percent oxygen by mask was initiated. Over the next thirty-six hours the subcutaneous crepitant neck mass diminished in size, restoring the normal anatomic contours. A chest roentgenogram 45 hours after admission no longer showed air above the diaphragm; some air remained in the upper mediastinum and the cervical region (Figure 2). The patient was discharged asymptomatic. Thirty-four days later she had no complaints and there were no abnormal physical findings.



Figure 2. Chest roentgenogram, thirty-five hours after Figure 1, PA view, revealing residual air in the upper mediastinum and the neck. Supradiaphragmatic air has disappeared.

### Discussion

Spontaneous pneumomediastinum may be caused by diabetic hyperpnea,<sup>6</sup> by severe coughing,<sup>7</sup> or by screaming.<sup>8</sup> It has been associated with pleasure-seeking valsalva maneuvers while smoking marijuana and heroin,<sup>9, 10</sup> and, more recently, with forceful breath-holding in order to attain a rapid "high" with the free-base form of cocaine alkaloid called crack.<sup>11, 12</sup> Pneumomediastinum is a rare complication of parturition, it usually occurs in primiparous women.<sup>13-15</sup> Its incidence has been variously reported between 1:2000 and 1:100,000 deliveries.<sup>13</sup>

A stabbing precordial pain is the principal complaint in 80-90 percent of the cases.<sup>16</sup> The pain may also be retrosternal and dull. It may mimic myocardial infarction or pericarditis, it may radiate to the shoulders, neck, and the upper arms. In some patients, the pain is aggravated by deep breathing or swallowing. Dysphagia or a sore throat is at times the principal complaint.<sup>4, 5</sup> Crepitation is frequently noted in the lower neck, but, depending on

the size of the air leak, it may take hours to develop or may be absent. A crepitant or crunching sound synchronous with systole (Hamman's sign) may be heard over the precordial area in about 50% of cases.<sup>16</sup>

The final common pathway of spontaneous pneumomediastinum is the production of high intraalveolar pressures. The pressure gradient generated between alveoli and the perivascular interstitium causes air to dissect proximally to the hilum and along fascial planes to cervical, subcutaneous, and retroperitoneal soft tissue spaces.<sup>16, 17</sup> Subpleural dissection may lead to pneumothorax.<sup>17, 18</sup>

The chest roentgenogram provides indisputable evidence of the clinical event. Sharp lines of increased lucency may outline one or both of the cardiac borders and may track to the neck along fascial planes. Subtle findings in the porteroanterior projection may be missed if a lateral view is not obtained. As shown by this case, the air may dissect through the mediastinum under the pleura covering the diaphragm creating a linear supradiaphragmatic collection of air easily mistaken for a small pneumothorax, the "extrapleural air sign".<sup>16</sup> When pneumothorax is present decubitus films will demonstrate a shift of the air column from the supradiaphragmatic level to the uppermost side of the pleural space.

No specific treatment for pneumomediastinum is usually considered necessary. There is some data to suggest that reducing the arterial partial pressure of nitrogen, by administering high concentrations of oxygen, may hasten the absorption of the trapped gas.<sup>19, 20</sup> The reduced nitrogen tension in the capillaries of the tissue surrounding sequestered air creates a gas bubble to capillary pressure gradient which enhances absorption.

**Resumen:** Una joven de 15 años desarrolló un severo dolor subesternal durante el último esfuerzo expulsivo al dar a luz a su primer hijo. Poco tiempo después se notó una hinchazón crêçiente, crepitante, al nivel supraesternal. La radiografía del tórax demostró un neumomediastino y enfisema subcutáneo. El aire disectó del mediastino al cuello y entre la pleura parietal y el músculo del diafragma. Se repasan las causas y la fisiopatología del neumomediastino espontáneo y el uso de altas concentraciones de oxígeno en su manejo.

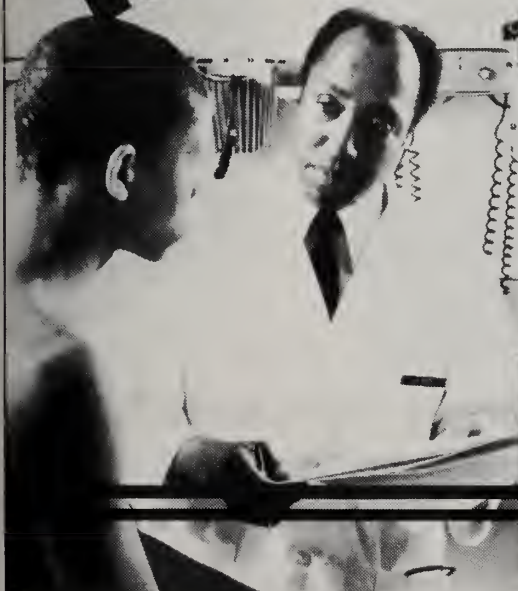
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# Malignant Fibrous Histiocytoma of the Lung

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**Abstract:** Malignant fibrous histiocytoma is the most common soft tissue sarcoma of adult life with a peak age of incidence in the sixth and seventh decades. This tumor rarely occurs in children. Our review of the literature found no reports of the tumor occurring in children as a primary lesion of the lung.

**M**alignant fibrous histiocytoma (MFH) is a pleomorphic mesenchymal sarcoma of older adults with a peak age of incidence in the sixth and seventh decades of life.<sup>1</sup> The most common primary sites are the extremities and retroperitoneum.<sup>2</sup> This tumor is rare in children and we could not find any references to its occurrence as a primary lung lesion.

We describe the case of a 10 y/o girl with malignant fibrous histiocytoma of lung without evidence of a primary tumor in any other site.

## Case Report

The patient is a 10 y/o female with history of bronchial asthma. In a routine physical exam she was suspected of

having scoliosis. Films of the thoracic spine revealed the presence of a 5.0 cm. by 4.5 cm. round mass in the left lower lobe. Chest films done confirmed the findings (Figs. 1A and 1B). A chest CT scan (Fig. 2) showed a fairly homogeneous density occupying the vicinity of the superior segment of the left lower lobe (LLL) and intimately related to central bronchi. Some areas of the lesion appeared to be cystic. Diagnostic considerations at that time were lung sequestration, bronchopulmonary foregut malformation and hamartoma. An arteriogram demonstrated a non-vascular lesion of the lung. Thoracotomy with resection of the superior segment of the LLL was done and the preliminary pathologic report was lung hamartoma. The final pathologic diagnosis, however, was malignant fibrous histiocytoma.

The child underwent CT scans of the brain, abdomen and pelvis which were normal. A bone scan showed no evidence of a primary bone lesion or metastatic disease. In view of the pathologic diagnosis, the patient had a second thoracotomy with left lower lobe lobectomy. Revision of hilar and mediastinal nodes at that time showed no evidence of metastatic disease.



Figure 1-A) Shows a soft tissue density projecting over left paraspinal region.



Figure 1-b) Examination shows the round density to be in the superior segment of the left lower lobe.

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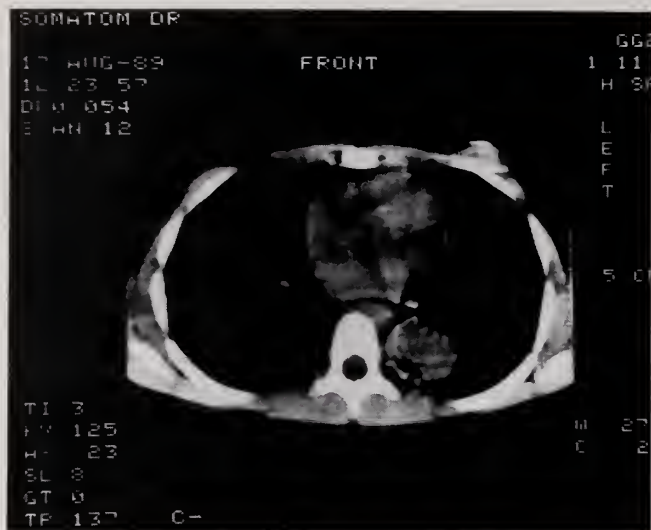


Figure 2. Chest CT Scan shower fairly homogeneous lesion with cystic component in its posteromedial aspect. Note its external relation to the central brach.

### Discussion

In children, the most common malignant lesions in lung are metastatic. In the first five years of life the most common are from metastatic Wilm's tumor and rhabdomyosarcoma. Later on, osteosarcoma and Ewing's sarcoma become more frequent.

Until recently, malignant fibrous histiocytoma was frequently confused histologically with rhabdomyosarcoma, pleomorphic sarcomas, fibrosarcoma and other sarcomas.<sup>1, 3</sup> MFH is considered to be a type of sarcoma of primitive mesenchymal cell origin. Therefore, it may potentially arise from any part of the body.<sup>4</sup>

Very little is known of the behavior of this type of lesion when it occurs as a primary lung lesion. The only reference of its natural history comes from its incidence in extremities and retroperitoneum.<sup>3</sup> The reported rate of survival is significantly affected by the location, the depth of the lesion, the size and the inflammatory component of the lesion.<sup>5</sup> At the moment, radical surgery of deep tumors appears to significantly delay progression of the disease, although survival was not improved. Chemotherapy and radiotherapy have also been used but with very ineffective results.<sup>1, 5</sup> The average survival rate at present is one year.<sup>1</sup>

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**Description:** Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

**Action:** Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

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**Indications:** Yocon<sup>®</sup> is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

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**Warning:** Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

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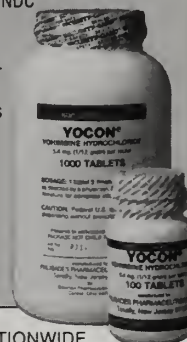
**Dosage and Administration:** Experimental dosage reported in treatment of erectile impotence.<sup>1,3,4</sup> 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.<sup>3</sup>

**How Supplied:** Oral tablets of Yocon<sup>®</sup> 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

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# CARTAS AL EDITOR

## Racionamiento de Servicios en el Hospital Pediátrico

**E**l Hospital Pediátrico Universitario no tiene electores o votantes que aboguen por dicha institución. Esto obedece a su localización y al hecho de que ofrece tratamiento a todos los niños de Puerto Rico y no existe ningún tipo de relación ulterior luego que los pacientes reciben el tratamiento. De igual forma como se ha expresado recientemente y cínicamente, los niños no votan.

Durante los últimos seis años el Hospital Pediátrico ha sido administrado por el Recinto de Ciencias Médicas y su Junta de Directores la constituyen varios miembros del Consejo de Educación Superior y el Rector del Recinto de Ciencias Médicas. La institución ha estado operando con déficit, ya que la cantidad asignada por el Departamento de Salud no es suficiente para cubrir todos los servicios ofrecidos a la población infantil de nuestra Isla. En adición a los servicios médicos que allí se ofrecen, el Hospital Pediátrico es el taller de enseñanza para estudiantes de medicina y de múltiples programas de adiestramiento de médicos en especialidades y subespecialidades tales como Pediatría, Cirugía Pediátrica, Neurocirugía, Ortopedia, Urología, Otorlaringología, Odontología, Anestesia, Medicina Física y otras. La magnitud del servicio y de la enseñanza que allí se ofrece aparentemente no ha sido captada en toda su dimensión por su Junta de Directores.

Durante los dos últimos años se han cerrado varias de las áreas de pacientes tanto en el Departamento de Cirugía como en el de Pediatría. Al presente solo están funcionando sus unidades de cuidado intensivo y un piso para pacientes. El número de operaciones realizadas por los subespecialistas quirúrgicos ha disminuido. En efecto, al negar los servicios, estamos racionando los mismos sin admitirlo públicamente. Esta reducción en los servicios no solo deja sin tratamiento a los pacientes sino que puede poner en peligro la acreditación de los programas de adiestramiento de la Institución.

El propuesto traspaso al Hospital Universitario conllevará una mayor reducción en los servicios que se ofrecen a nuestros niños, en particular a los pacientes indigentes, quienes son cautivos del sistema de salud pública de Puerto Rico y no pueden acudir a ninguna otra institución en busca de servicios médicos de excelencia.

Existe una seria preocupación entre la Facultad Médica del Hospital Pediátrico ante el inminente tras-

paso del Hospital Pediátrico al Departamento de Salud. El personal no docente también se opone a dicho traspaso pues perderían los derechos adquiridos a través de los convenios firmados con la Universidad de Puerto Rico.

Los ahorros que se lograrían al convertir al Hospital Pediátrico en el Departamento de Pediatría del Hospital Universitario de Adultos serían exiguos, pues solo se ahorrarían el sueldo del Director Ejecutivo, Administrador, Director de Presupuesto y Director de la Oficina de Personal. Comparados con el déficit presupuestario, que es de millones, dichos ahorros son insignificantes. Para realmente reducir el déficit se tendría que recurrir a continuar con el racionamiento de servicios, debido a la desproporción exagerada por servicios y los pocos recursos disponibles para los niños de Puerto Rico. Esto último equivaldría a castigar o perjudicar un segmento de la población, precisamente el más indefenso.

Recuerden que la grandeza o mezquindad de los pueblos se mide a base de como trata a sus niños, ancianos y desamparados. El continuar reduciendo los servicios a nuestros niños constituye el maltrato colectivo más severo, injustificado e impropio que se puede infligir a la población infantil que carece de recursos económicos adecuados.

Treinta años luego de establecida la Escuela de Medicina de la Universidad de Puerto Rico carecemos de un Hospital Universitario adecuado para la enseñanza, según estaba contemplado en la ley que creó la Escuela de Medicina. El recientemente designado Presidente de la Universidad de Puerto Rico pretende transferir las futuras deficiencias económicas al Departamento de Salud. Su recomendación de traspasar el Hospital Pediátrico al Departamento de Salud es una admisión de fracaso de la presente administración universitaria al no poder manejar una institución hospitalaria pequeña. Este fracaso administrativo será detrimental para el futuro desarrollo de una práctica geográfica a tiempo completo y a la deseabilidad de que nuestra Escuela de Medicina pueda eventualmente tener su propio Hospital Universitario, el cual necesariamente será más grande y complejo que el Hospital Pediátrico.

Deben ustedes, nuestros lectores conocer que alrededor del 60% de los sueldos de la Escuela de Medicina los

provee el Departamento de Salud. Esto demuestra que los anteriores Consejales ni el actual Consejo de Educación Superior han asumido la responsabilidad de administrar la propia Escuela de Medicina, menos aún desean o le interesa continuar administrando el Hospital Pediátrico. Su interés primordial al presente es cerrar el presupuesto de la Universidad de Puerto Rico sin déficit y pretenden que el Departamento de Salud, otra agencia gubernamental asuma la carga económica.

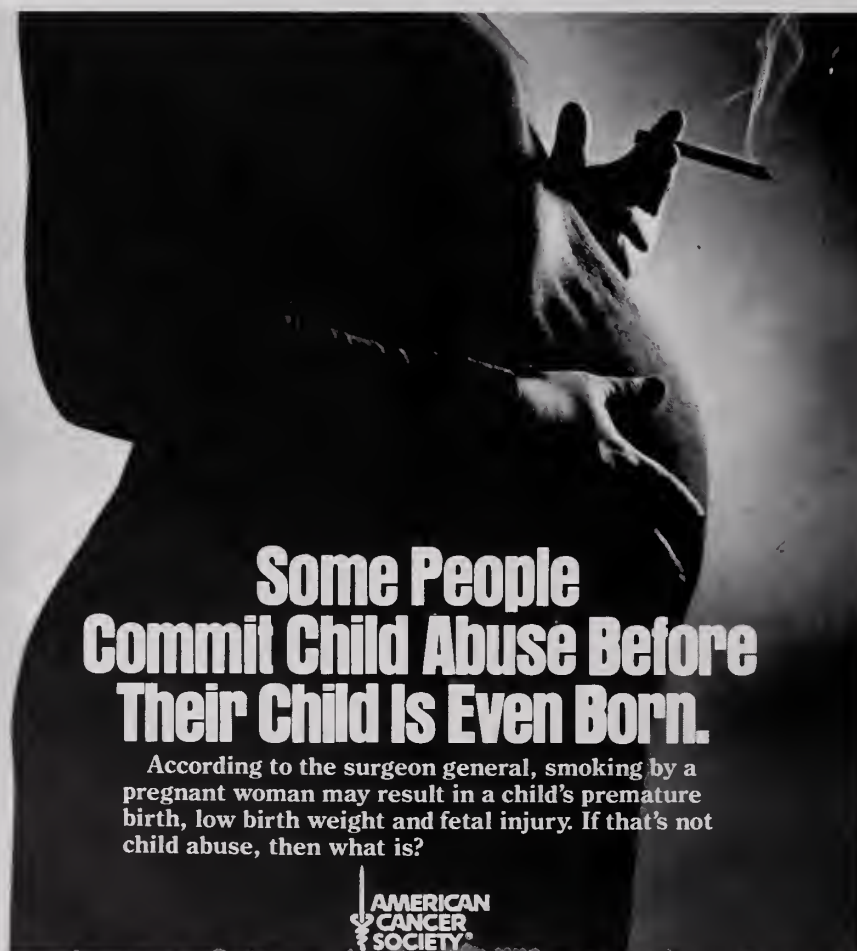
El Hospital Pediátrico requiere una atención de alta prioridad de parte del Gobierno de Puerto Rico para no solo continuar como una institución hospitalaria, sino expandir sus servicios, construirle salas de operaciones de niños y hacerlo competitivo con otras instituciones, atrayendo pacientes privados que contribuyan al mejoramiento de los servicios que allí se ofrecen. Se debe evitar la duplicación de los mismos servicios en otras instituciones públicas si no existen los recursos económicos adecuados. El Hospital Pediátrico debe gradualmente independizarse del Centro Médico. Al presente tanto el Hospital Pediátrico como el Hospital Universitario de Adultos son cautivos del Centro Médico.

Aparentemente las prioridades de nuestro gobierno están torcidas y están dirigidas a otros grupos generacionales o es que no se atreven admitir que carecemos de recursos adecuados para ofrecer servicios médicos a la población en general. Al final del año pasado el Hospital

Pediátrico estuvo cerrado exactamente por un mes debido a un conflicto huelgario. Excepto por casos anecdotales nadie sabe que le ocurrió a los niños gravemente enfermos que necesitaron servicios médicos. La Facultad del Pediátrico improvisó algunas medidas de emergencia para minimizar el impacto negativo en los pacientes. Se debe evitar por todos los medios disponibles que ocurra otro paro como resultado de los planes de traspasar el Hospital Pediátrico al Departamento de Salud. Otro paro huelgario en el Hospital Pediátrico implicaría una confabulación para seguir maltratando colectivamente a nuestros niños.

Las agencias gubernamentales y el propio gobierno central deben ser juzgados por el pueblo y exigirle se asignen los recursos necesarios para continuar el funcionamiento de Hospital Pediátrico Universitario a toda capacidad como lo requiere nuestra población infantil.

**Enrique Vázquez Quintana, MD, FACS**  
Catedrático de Cirugía  
Recinto de Ciencias Médicas  
Universidad de Puerto Rico







# MEDICAL ASPECTS OF NUTRITION

## Nutrition and Athletic Performance\*

P.M. Kris-Etherton, Ph. D, RD\*\*

Nutrition holds a time-honored place in the annals of competitive sport. Historically, athletes have been interested in the relationship of diet to athletic performance. Only recently, however, have the effects of nutrition on athletic performance become a topic of scientific inquiry. The following report summarizes some major nutritional concerns of athletes.

### Energy

Energy requirements of athletes are influenced by the type of sport, duration of exercise, fitness level, body weight and other factors.<sup>1-3</sup> In general, as the level of physical activity increases, so do energy needs and caloric intake. A small female archer may require only 2,000 calories/day, whereas some athletes may consume at least five times more energy.<sup>4</sup> Many elite athletes participating in sports, such as swimming, weight lifting and wrestling, consume between 2,000-4,500 calories/day. Elite female athletes competing in figure skating, judo and gymnastics consume only 1,700-1,800 calories/day,<sup>5</sup> an amount comparable to that of a typical American woman. The theory that some elite athletes are metabolically efficient is based on some studies that have shown that calorie intake of elite athletes is lower than expected.<sup>6</sup> Further studies are necessary to resolve this issue since these findings have not been consistently reported.

Repetitive cycles of weight gain and loss occur in many athletes within a competitive season and between seasons but most notably in those who compete best at a relatively low body weight. It is not uncommon for collegiate wrestlers to gain from 4-8 pounds after weigh-in but prior to competition, with some weighing up to 17 pounds more the morning after their match.<sup>4</sup> Some wrestlers lose 20-40 pounds prior to the season to qualify to wrestle in certain weight classes. Wrestlers who were classified as weight cyclers had a 12% lower resting metabolic rate

than noncyclers.<sup>7</sup> These findings suggest a metabolic efficiency that results from repeated dieting. Another consequence of dieting and weight loss in amateur wrestlers is low-serum testosterone levels.<sup>8</sup> The mononuclear phagocyte system, a major defense complex against certain microorganisms, has been reported to be reduced in athletes who lose weight by calorie restriction.<sup>9</sup> However, the clinical significance of these observations remains to be clarified.

### The Macronutrients: Carbohydrate, Protein and Fat

The recommended diet for an athlete is high in carbohydrate (CHO) (50%-55% of calories), correspondingly lower in fat (30% of calories) and adequate in protein (15%-20% of calories).<sup>2</sup> Similar dietary recommendations have been made for all Americans by the United States Department of Agriculture (Dietary Guidelines) the Surgeon General and the Food and Nutrition Board of the National Academy of Sciences.<sup>10-12</sup>

It is well recognized that CHO, protein and fat are all utilized as fuel sources during exercise.<sup>13</sup> The type and duration of activity determine the utilization of fuel sources. Short-term, high-intensity activities, such as the discus throw, high jump or diving, rely on anaerobic fuel sources. Longer-term activities of lesser intensity, such as long-distance running and cross-country skiing, require aerobic energy sources. Some activities, such as tennis, basketball and soccer, utilize both.

CHO is a unique fuel source for exercise because it can be metabolized by both aerobic and anaerobic pathways. Fat and protein are metabolized only by aerobic pathways. During the initial phase of exercise (<2 minutes), anaerobic metabolism is the principal source of energy; however, as exercise continues (>10 minutes), there is a shift toward aerobic metabolism which then becomes the primary fuel source.<sup>14</sup> CHO and fat are the predominant energy sources for exercise, while protein only contributes 5%-10% of the fuel during prolonged physical activity.<sup>15</sup> A habitual diet high in CHO promotes muscle glycogen storage which, in turn, enhances endurance. Moreover, a diet high in CHO compared to a low-CHO

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diet prevents sustained exercise-induced muscle glycogen storage which, in turn, enhances endurance. Moreover, a diet high in CHO compared to a low-CHO diet prevents sustained exercise-induced muscle glycogen depletion. Muscle glycogen stores are replenished to pre-exercise levels in individuals consuming a high-, but not a low-, CHO diet.<sup>16</sup>

In general, CHO ingested *prior to competition* has been shown to have no effect on performance. Two studies, however, have reported beneficial effects of CHO supplementation on performance in cyclists and soccer players.<sup>17</sup> Pre-exercise candy bar consumption, previously thought to adversely effect performance, does not cause premature fatigue and decreased endurance.<sup>18</sup> CHO supplementation *during prolonged strenuous exercise* has been shown to improve performance.<sup>17</sup> Exogenous glucose is oxidized as the primary energy source, sparing muscle glycogen and delaying fatigue. Very dilute CHO solutions ( $\leq 10\%$  sugar) are emptied from the stomach and absorbed from the intestine as rapidly as water. They provide fuel, help control body temperature and maintain plasma volume during exercise. Sufficient dietary CHO is essential *after exercise* to replenish muscle glycogen stores. It is important that CHO be ingested within 2 hours after prolonged strenuous exercise (and preferably within about 20 minutes) because glycogen synthetic rates are about 50% higher than at 2-4 hours following exercise.<sup>17</sup> Athletes should consume at least 1.5 g of CHO/kg body weight shortly after exercise and again 60 minutes after exercise. For a 50 kg woman (110 pounds), that means about 2 cups of apple juice or 1 cup of corn flakes with 1 medium banana and 1 cup of skim milk. Since appetite is suppressed after exercise, the quantity of CHO recommended can be sizable. Concentrated sources of CHO can be useful to meet this recommendation.

CHO loading, a technique used to increase muscle glycogen stores 2- to 3-fold, is effective in maximizing endurance.<sup>2</sup> In a modified regimen seven days prior to competition, athletes consume 350 g of CHO/day and during the 72 hours prior to competition, 525-550 g of CHO/day is recommended. Avoidance of moderate-heavy exertion 1-2 days before competition and a tapered rest regimen are also recommended.

Recent information suggests that athletes (especially those participating in endurance sports) need more protein—approximately 1.0 g of protein/kg body weight daily and perhaps as much as 50% more than the Recommended Dietary Allowance (RDA).<sup>15</sup> Further research is necessary to establish the protein requirements of athletes since experiments conducted to date have not controlled for the time of sample collection relative to the exercise bout, energy and protein intake and status and exercise intensity.<sup>19</sup>

Athletes who usually consume a high-calorie diet typically meet their protein needs.<sup>4</sup> However, due to a low-energy intake or a high-CHO intake, protein consumption may not be adequate for athletes in negative energy balance.<sup>19</sup> Athletes can easily meet their protein needs by following a balanced diet instead of taking protein mega-supplements. Hypercalcuria (extra calcium in urine) occurs when protein intake increases from 0.8-

2.0 g of protein/kg body weight/day.<sup>20</sup> Dehydration is a concern with protein supplements since excess nitrogen and, hence, water are excreted, increasing the kidney workload.<sup>20</sup> Some athletes take amino acid supplements believing that they build and repair muscle, reduce fat and provide energy. Arginine and ornithine supplements, the new rage among body builders, are promoted as growth hormone secretagogues.<sup>20</sup> There is no scientific basis for any of these claims.

A recent study reported that elite male marathon runners and rowers had the lowest fat intake (about 35% of calories from fat) compared to other elite male athletes and nonathletes in Germany.<sup>22</sup> Elite cyclists, biathlon athletes and wrestlers consumed diets with approximately 37% of calories from fat. Fat contributed about 42% of calories to swimmers' diets. Wrestlers consumed more calories from fat (about 46%) than any other group studied. While differences in fat intake among selected elite athletes were reported, all groups consumed more calories from fat than is presently recommended. Information on appropriate food choices is needed to help athletes meet energy, protein and CHO needs while reducing fat intake to less than 30% of calories.

### Vitamins and Minerals

Vitamins and minerals are important for nutrient and oxidative metabolism.<sup>2</sup> Hence, optimal vitamin and mineral status is important for top exercise performance. While a vitamin or mineral deficiency can impair athletic performance, there is no evidence that nutrient supplementation in excess of the RDA is beneficial.<sup>23</sup> Exercise, however, may increase nutrient requirements for certain vitamins, such as vitamin C and riboflavin, in marginally deficient individuals.<sup>23</sup> Increases in vitamin B<sub>6</sub> metabolism after exercise have been noted in young men.<sup>24</sup> These changes may be the result of pyridoxal phosphate release from glycogen phosphorylase to supply glucose to the glucose-alanine cycle. While one study<sup>25</sup> reported a 60%-84% supplement use among athletes, multivitamin-mineral supplementation is not recommended for athletes except when energy intake is very low.<sup>2</sup>

The habitual diets of many American women are low in both calcium and iron, thereby making these nutrients of special concern to athletes. Calcium is important for maintaining bone mass and muscle contraction. Weight-bearing exercise, such as walking, running and racket sports, promote osteogenesis. Bone mineral density is increased in bones subjected to mechanical stress.<sup>26</sup> Nonweight-bearing exercise may be beneficial for inactive individuals to strengthen and protect bone by strengthening muscle. The type, intensity, duration and frequency of exercise to achieve optimum bone mineral status are yet to be determined.<sup>3</sup>

Athletic amenorrhea (a condition in which intense training leads to the cessation of menstruation in 2%-37% of female athletes) accelerates bone loss especially in the lumbar spine. Studies have shown that vertebral bone density is 8%-14% lower in amenorrheic athletes.<sup>27, 28</sup> Resumption of menses in amenorrheic athletes led to a 6.3% increase in vertebral bone mineral density. There is some question, however, whether or not vertebral bone



mineral density returns to normal. Interestingly, exercise reduces bone loss in anorexic women with amenorrhea.<sup>29</sup> Women with exercise-induced amenorrhea may require 1,000-1,500 mg of calcium/day. Low energy intake may warrant calcium supplementation.

Iron-deficiency anemia and likely marginal iron deficiency impair athletic performance by reducing the oxygen-carrying capacity of blood and inhibiting mitochondrial enzyme function. Iron needs appear to be higher in athletes because of increased iron losses presumably from increased red blood cell destruction, gastrointestinal blood loss, iron loss in sweat and decreased iron absorption.<sup>30</sup> Estimates of the incidence of poor iron status in female runners range from 20%-80%.<sup>31</sup> Female athletes frequently have difficulty meeting their iron needs because of caloric restriction, avoidance of meat and an extreme emphasis on CHO intake. Iron status should be periodically monitored in female athletes and if status and intake continue to be suboptimal, an iron supplement is recommended.

### Fluids and Electrolytes

Dehydration, a potentially lifethreatening condition, compromises athletic performance. Since the thirst mechanism is blunted with exercise<sup>1, 2</sup> it is important for athletes and trainers to monitor and meet fluid needs. Cool plain water, the recommended beverage for fluid replacement in moderate exercise, should be drunk before, during and after exercise.<sup>2</sup> Athletes should note weight changes from fluid losses during exercise and drink two cups of water for every pound lost.<sup>2, 16</sup> Commercial beverages that supply CHO may be suggested for endurance athletes during exercise; however, the CHO or sugar concentration of these beverages should not exceed 10%. Electrolytes (sodium, potassium and chloride) lost in sweat usually can be replaced by diet. Hyponatremia (low sodium levels) can be a problem for athletes who sweat profusely. For endurance athletes exercising under extreme environmental conditions, commercial sports beverages containing electrolytes can help to replace losses.

### Nutrition Fads

In their search for any means to improve their athletic ability, athletes and coaches often fall prey to nutrition fads. The variety of special products available to athletes is staggering<sup>32</sup> with little or no scientific basis for their efficacy. Manufacturers encourage athletes to consume "energizers," "performance supplements," "vitamin/mineral power-pack supplements," "glycogen replacers," products that produce "muscular acceleration" and others. Uninformed athletes succumb to the lure of athletic achievement by consuming a number of these products at outrageous costs. For example, if athletes take just five different products per day (at the dose recommended by the manufacturer), they may spend \$10-\$15 per day or \$70-\$105 per week on unnecessary supplements. Furthermore, some athletes take two to three times the manufacturer's recommended dosage of these products. The widespread abuse has created an urgent need to develop effective programs that provide

accurate nutrition information to athletes. Realistically, this is a challenging undertaking because of the perceived validity of personal testimonials touting the efficacy of these supplements.

### Summary

- Energy, CHO and possibly protein needs are higher for athletes than for typical persons.
- CHO supplementation during and after exercise is important for endurance athletes.
- A balanced diet, adequate in calories, can meet the vitamin and mineral needs of virtually all athletes.
- Athletes must be aware of maintaining an optimum hydration status.
- Intensive nutrition education efforts are needed to combat to combat quackery and fads that are targeted to athletes.

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More information is available from the Penn State Nutrition Center, Benedict House, The Pennsylvania State University, University Park, PA 16802 and the Sports and Cardiovascular Practice Group of The American Dietetic Association, 216 West Jackson Boulevard, Suite 800, Chicago, IL 60606.

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For the past two decades, a dramatic worldwide rise in smoking has occurred and health experts predict within 20 more years, the deadly impact of that trend will become apparent, a report in the *Journal of the American Medical Association* concludes.

A few observations:

- 200 million children younger than 20 years will die from tobacco use
- Worldwide, lung cancer rates will jump to 2 million by the year 2000
- In 1986, an estimated 1 billion people smoked 5 trillion cigarettes

"To maintain and expand markets for their ongoing growth of tobacco leaf and manufactured tobacco products, multinational tobacco conglomerates in the United States, Great Britain, and West Germany, however, have responded by increasingly seeking favorable markets in countries where demand remains or has the potential for becoming high," according to a report on the worldwide smoking epidemic by the AMA Council on Scientific Affairs (CSA).

Every year, nearly 2.5 million "excessive or premature deaths" — nearly one in every twenty deaths in the world— are linked to tobacco use, according to the CSA report.

Faced with a declining domestic market, U.S. tobacco companies have turned abroad, enjoying significant growth in the process. The increasing affluence in Asian countries, including Japan, Taiwan and South Korea partially is reflected in a 75 percent hike in U.S. tobacco exports to Asia in 1988, the report continues.

More U.S. tobacco exports lead to more and new brands of cigarettes which, in turn, leads to lower prices. "In countries where low per capita consumption of cigarettes is due to lack of disposable income, lower cigarette prices can lead to an increase in tobacco consumption," says the council.

"The tobacco industry, ignoring long-term costs of medical care, loss of productivity from tobacco-attributable morbidity and mortality, loss of land use for growth of other crops, and problems of deforestation,

including global warming, continues to promote tobacco as an excellent cash crop," the report continues.

The U.S. leads the world in tobacco exports, followed by Brazil, Greece, Italy and Zimbabwe. In 1987, the U.S. made 689 billion cigarettes, second only to the annual production of 1.4 trillion in China, the report says.

In several countries, governments control and profit from the tobacco companies and, as a result, often there aren't many incentives to establish antitobacco campaigns, according to the report. By 1986, a total of 55 countries enacted laws controlling tobacco advertising —20 with complete bans, 15 with strong partial bans and 20 (including the U.S.) with moderate bans, the report says.

Among the CSA's recommendations:

- Urge the U.S. government to alter its trade policies regarding tobacco
- Impose health warning labels on cigarette packages for export
- Support greater World Health Organization anti-tobacco efforts
- Encourage physician involvement in antitobacco projects in developing countries

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## INTERNATIONALLY, CESAREAN SECTION RATES RISE

As in the U.S., rates of cesarean section rose around the world from 1975 to 1986, according to a study in *Journal of the American Medical Association*.

"For most countries, rates of cesarean section have risen as operative vaginal delivery rates have fallen," writes Francis C. Notzon, PhD, to the National Center for Health Statistics, Hyattsville, Md.

Notzon studied cesarean rates in 21 countries and regions. They included Australia, Bavaria, Brazil, Canada, Czechoslovakia, Denmark, England and Wales, Greece, Hungary, Italy, Japan, the Netherlands, New Zealand, Norway, Portugal, Puerto Rico, Scotland, Spain, Sweden, Switzerland, and the United States.

Brazil had the highest rate of cesarean deliveries per 100 hospital deliveries with nearly 32 per 100 from 1981 through 1986, according to the study. Puerto Rico had the second highest cesarean rate with 29 per 100 hospital deliveries; the U.S. was third with 23 per 100. Czechoslovakia and Japan were last with a rate of only seven per 100.

"Comparing the 1985 cesarean rates with those for

previous years," Notzon writes, "it is clear that the rate of increase slackened in most countries after 1980." For all countries and regions, cesareans increased an average of 8.7 percent a year from 1976 to 1980; from 1981 to 1985, the rate of increase was only 4.6 percent. Denmark showed the largest decline, from 11.3 percent to 4.6 percent; the U.S. rate of increase dropped from 8.3 percent to 6.3 percent. In Sweden, cesarean rates decreased an average of 1 percent a year from 1981-85.

"Nevertheless, it would appear that continued increases in obstetric interventions may lead to only marginal improvements in birth outcomes," Notzon writes. "A comparison of 1985 national rates of intervention and measures of birth outcome found no significant relationship between the two. While such ecological comparisons are imperfect at best, this does indicate that low levels of early infant mortality can be achieved in some populations despite a low rate of cesarean deliveries."

Given the cost implications of cesarean deliveries, Notzon suggests "a careful review of the Swedish experience, including both the rise in cesareans and the current period of stability, might prove useful to other nations interested in stemming the rise in their own cesarean rate."

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### INTERNATIONAL HEALTH AND THE HUMAN GENOME PROJECT

By mapping out the genetic map of the human body, researchers believe great strides can be made "in their assault on disease," according to a commentary in the *Journal of the American Medical Association*. Written by James D. Watson, PhD, and Robert Mullan Cook-Deegan, MD, of the National Center for Human Genome Research, National Institutes of Health, Bethesda, Md., the commentary says technical progress has been rapid since the project began and when complete genetic maps become available "extensive sequencing data will have an impact on the diseases that plague the developing world, in addition to those diseases prevalent in economically developed nations," the authors write. "If genetic tools created by the genome project prove useful over the next five years, then special efforts to use them in the study of disease prevalent in the developing world must receive serious attention. Genetics will not explain everything, but having access to the genetic instruction set is an essential step to understanding any of these disease in detail."

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### AMA PROFILE OF ADOLESCENT HEALTH

The American Medical Association recently released the first in a three-volume series on adolescent health entitled, "America's Adolescents: How Healthy Are

They?," detailing the current threats to the health of American youth. The publication represents a new resource in planning, advocacy, teaching, and community education for those persons who work with or for adolescents.

Medical and social science research on adolescents has revealed two disturbing trends, according to the authors. First, many health problems are affecting adolescents at younger ages, and youth are often simultaneously involved in several health-threatening behaviors such as drug use, delinquency, unprotected sex and sex with multiple partners. Approximately 25 percent of adolescents lead "high risk" lifestyles that result in injury, hospitalization, or other unhealthy consequences, say the authors.

The disturbing trends in adolescent health include:

- Homicides have doubled among 10- to 14-year-olds during the past 20 years and are especially high among blacks.
- During the past 20 years, suicides tripled among 10- to 14-year-olds and doubled among 15- to 19-year-olds. Whites are three times more likely than blacks to die from suicide.
- By the time they are 18 years old, 65 percent of boys and 51 percent of girls are sexually active. Approximately 50 percent of American adolescents do not use contraceptives the first time they have intercourse. Half of premarital pregnancies occur within the first six months after sexual initiation.
- Approximately 20 percent of people identified as having AIDS are between 20 and 29 years of age. Because it takes an estimated five to ten years for the HIV infection to result in AIDS, many young adults who have AIDS probably contracted the virus as adolescents.

### DEPRESSION, NOT VIRUS, SEEN AS CAUSE OF CHRONIC FATIGUE

New research suggests that depression, and not the Epstein-Barr virus (EBV), is the cause of chronic fatigue (CF) syndrome, according to an article in the *Journal of the American Medical Association*.

"We could identify no virologic data to support the hypothesis that replication of EBV is related to CF in patients with high EBV antibody titers," write Deborah Gold, MD, of the University of Washington School of Medicine, Seattle, and colleagues. Other investigations have noted an association between high EBV antibody titers and CF.

Gold and her colleagues found that patients with CF "had a strikingly higher rate of lifetime and current major depression than controls." They write "the association between CF and affective illness has been described in several recent studies, suggesting that depression may be the primary disorder in some patients."

Twenty-six patients were studied between 1985 and 1987. All had symptoms of fatigue, plus other complaints, including fever, weight loss and frequent upper-respiratory tract infections. Eighteen volunteers



with no medical complaints were recruited to function as a control group. Both groups were subject to an initial medical, serologic, virologic and psychiatric evaluation. Additionally, CF patients were tested at regular intervals for EBV.

CF patients who continued in the study stayed an average of 11.3 months. At the end of the study, four CF patients felt completely normal and had resumed preillness activity levels. Another eight were significantly improved. "The patients' assessment of improvement was supported by a 50 percent decrease in the number of symptoms compared with enrollment and by a significant increase in daily activities and/or exercise," the authors write.

"We found no correlation between EBV antibody titers and the severity of CF or its clinical course over time," they write. "We could demonstrate no significant differences in the prevalence of active EBV infection between our cohort and a control group."

However, the researchers found "that patients with CF had significantly more lifetime episodes of major depression and current major depression than controls."

"The findings of improvement in more than 50 percent of our patients over a fairly short duration of follow-up should be encouraging to physicians who care for patients with CF," conclude the authors.

*JAMA July 4, 1990*

#### NCI REPORT FINDS SCREENING MAMMOGRAPHY STILL UNDERUTILIZED

Women who are prime candidates for screening mammography aren't getting them, concludes a report in the *Journal of the American Medical Association*.

Older women don't seek mammography because they feel it is unnecessary or because their physicians do not recommend the procedure to them, according to the National Cancer Institute (NCI) Breast Cancer Screening Consortium, author of the report. Underutilization of breast cancer screening procedures—clinical breast examination and mammography—probably explains why death rates from breast cancer have not declined in the past 30 years, says the report.

"Low mammography rates may be due in part to physicians missing the clinical opportunity to explain the benefits of screening mammography to their eligible patients and to recommend that they undergo screening at regular intervals," the report says.

To evaluate current breast cancer screening use, the NCI consortium conducted studies in six areas: suburban Los Angeles, Calif.; eastern Massachusetts; Long Island, NY; eastern North Carolina; Philadelphia, PA, and surrounding counties; and four counties in Washington state. Data from these regions were compared with estimates of screening utilization from the 1987 National Health Interview Survey (NHIS), an ongoing survey of U.S. households conducted by the National Center for Health Statistics.

The report focuses on noninstitutionalized, non-Hispanic white women, aged 50 to 74 years, who did not have breast cancer. Data were obtained by telephone interview or by a mailed survey. The women were asked how much they knew about mammography and breast examination, if they had ever had a mammography, their usual source of health care, their educational and income levels, and other questions.

Over 90 percent of the women surveyed said they had regular sources of medical care, but only 46 percent to 76 percent said their breasts had been examined by a health care professional within the previous year. Only 25 percent to 41 percent said they had had a mammogram. This falls far short of NCI's stated goal: 80 percent of women aged 50 to 70 years would receive annual clinical breast examinations and screening mammograms by the year 2000.

In both the regional and national studies, poorer, less educated women had fewer mammograms than did women with higher incomes and more education, the report says.

The most common reason women gave for never having had a mammogram was that "they had not thought about it and/or there was no problem" with their breasts which would prompt them to seek medical attention, according to the report. The next most common reason was that their physicians had not recommended it. Most of the women surveyed had heard of mammography, but few indicated that cost or fear of radiation had prevented them from having the procedure.

"These seven studies show there is still a large gap between current breast cancer screening practice and the needs of women. The gap is particularly large for less educated and poorer women," the report says.

Mammography use would increase if physicians help their patients understand that such breast cancer screening is intended for older women without breast problems, and if they recommended the procedure while performing a clinical breast examination, the report concludes. Current NCI projects are aimed at increasing awareness and use of screening mammography through community-wide and physician education programs.

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#### STUDY: SMOKELESS TOBACCO THROWS BALLPLAYERS A DANGEROUS CURVE

One statistic you won't hear during tonight's All Star Game telecast is the rate of oral lesions among baseball players who use smokeless tobacco.

A study in the *Journal of the American Medical Association* finds ballplayers who use smokeless tobacco products—especially snuff—are at great risk of developing lesions in the mouth and gum problems.

Virginia L. Ernster, PhD, of the Department of Epidemiology and Biostatistics, University of California School of Medicine, San Francisco, and colleagues, studied the health effects of smokeless tobacco among 1,109 baseball players and coaches during 1988 spring training camp in Arizona. Seven major league teams and

their minor league affiliates participated in the study: the California Angels, Cleveland Indians, Milwaukee Brewers, Oakland Athletics, Seattle Mariners, San Francisco Giants, and Chicago Cubs.

The researcher gathered information on players' use of snuff—a pinch of finely ground tobacco usually held in place between the lower lip or cheek and the gum—and chewing tobacco—a coarse tobacco plug placed inside the cheek pouch. They studied the effects of these products on the oral mucosa, teeth and gums of the players as well as on blood pressure, pulse rate and cholesterol level.

Thirty-nine percent of those surveyed said they used smokeless tobacco within the past week, a much higher rate than that found in the general population, the authors say. Players began using smokeless tobacco at about age 18 and had used it, on average, for five years. About three times as many players used snuff (typically Copenhagen or Skoal brands) as chewing tobacco (Levi-Garrett or Redman brands). Only 4 percent of players and coaches were cigarette smokers.

All participants underwent a thorough oral examination. Among those who used smokeless tobacco in the past week, 46 percent had oral leukoplakia, a leathery white or red patch inside the cheek that may become cancerous. Snuff users were more likely to develop lesions (55.6 percent) than tobacco chewers (17.2 percent). Oral leukoplakia was present in only 1 percent of those who were not smokeless tobacco users.

Ninety-two players with lesions underwent biopsies, none of which were cancerous. The authors note that other studies have found a strong association between long term snuff use and oral cancer.

Age at first use and years of use were not risk factors for oral leukoplakia. But, the authors report, "there was a significant association of oral leukoplakia with hours of smokeless tobacco use per day. Persons who held tobacco in the mouth for 4 hours per day were approximately six times more likely to have oral leukoplakia than users who held tobacco in the mouth only 1 hour per day."

Although most players practiced good oral hygiene, users were more likely than nonusers to have receding gums and separation of gums from teeth in those areas of the mouth where the tobacco is usually held. Such "periodontal disease is unlikely to be reversible even with cessation of smokeless tobacco use," the authors write.

The researchers believe snuff is more likely to cause oral problems because it is held in one place in the mouth, whereas chewing tobacco moves more loosely in the mouth. Moreover, snuff products generally have higher levels of nicotine and carcinogenic substances than chewing tobacco.

Blood pressure, pulse rate and cholesterol levels were generally the same in users and nonusers of smokeless tobacco. The researchers were not surprised at these findings since players exercised frequently and were physically fit, "behavior that could minimize adverse effects of nicotine on the cardiovascular or lipid systems," they write.

Baseball had long been associated with smokeless tobacco, but times may be changing. "There seems to be an increased awareness within the sport of professional

baseball that smokeless tobacco use is undesirable. Our findings of increased risk of oral leukoplakia and periodontal disease support that view," conclude the authors.

*JAMA July 11, 1990*

### ONE MANUFACTURER'S TRYPTOPHAN TIED TO ILLNESSES

A study in Oregon of illnesses linked to tryptophan found that the amino acid health food supplement most patients purchased came from one Japanese manufacturer, according to an article in the *Journal of the American Medical Association*.

Tryptophan was pulled from the market after it was linked to Eosinophilia-Myalgia Syndrome (EMS) in 1989. EMS symptoms include muscle pain severe enough to limit normal activities.

The study examined whether tryptophan itself or a contaminant caused EMS. "Our findings indicate that the recent epidemic of EMS was caused by a contaminant or an alteration in a subset of tryptophan manufactured by a single company in Japan shortly before the outbreak began," write Laurence Slutsker, MD, of the Centers for Disease Control Division of Field Services, Epidemiology Program Office, Portland, Ore., and colleagues.

Six Japanese companies make all the health food supplement tryptophan sold in the U.S. After importation, the tryptophan passes through three or four intermediaries, including a wholesaler, tablet maker, encapsulator or distributor. The authors did not name the manufacturer of the tryptophan tied to EMS.

"We compared brand and source of tryptophan used by 58 patients with EMS with the brand and source of tryptophan used by 30 asymptomatic controls identified through a random telephone survey and 63 asymptomatic controls who contacted the Oregon Health Division voluntarily," they write.

The study found that "45 (98 percent) of 46 cases had taken a product made by one manufacturer, compared with three (30 percent) of 10 telephone survey controls and 15 EMS with tryptophan from one manufacturer makes it unlikely that tryptophan itself caused illness," they write.

"Current analytic efforts are directed toward identifying this contaminant," they say. "Timely identification may promote understanding of the pathophysiologic characteristics of EMS and may suggest therapies, facilitate the return of uncontaminated tryptophan to the market, and increase our knowledge about the pathogenesis of other connective-tissue disease."

*JAMA July 11, 1990*

### PROGESTERONE SUPPOSITORIES NOT EFFECTIVE PMS THERAPY: STUDY

A popular treatment for premenstrual syndrome (PMS) has been shown to be ineffective in a study in the



### *Journal of the American Medical Association.*

Comparing progesterone suppositories to placebo, Ellen Freeman, PhD, of the Department of Obstetrics/Gynecology, Hospital of the University of Pennsylvania, Philadelphia, and colleagues, found no difference between the two treatments in relieving PMS symptoms.

"The evidence from this study that progesterone suppositories have no clinically significant therapeutic effect greater than that of placebo for premenstrual symptoms should turn investigation to other treatments for this distressing disorder affecting the lives of many women," the authors conclude.

This study is the largest and best controlled investigation to date of the effects of progesterone and placebo on treating PMS.

The researchers studied 168 women, average age 34 years, who had suffered PMS symptoms for approximately eight years. Seventy percent were married, 63 percent had one or more children, and 65 percent were employed.

All women underwent a four-month "washout" (pretreatment) phase during which they kept a daily record of their symptoms. They then received both progesterone and placebo vaginal suppositories, each for two consecutive menstrual cycles. Daily records of symptoms also were kept during the treatment phase.

After the washout phase, medication was taken on days 16 through 28 of the menstrual cycle (day 1 is the first day of menses). The women inserted one 400 mg suppository (either progesterone or placebo) vaginally each morning for one cycle, increasing to two suppositories or 800 mg (one 400 mg suppository in the morning and at night) for the second cycle. Patients then switched to the other treatment in a double-blind, crossover study design.

No differences were found in premenstrual symptoms between women receiving progesterone and placebo in the two treatment cycles before the crossover. After the crossover, women who switched from placebo to progesterone worsened in the third cycle, while those who switched from progesterone to placebo reported no change in symptoms. Both groups reported their symptoms decreased in cycle four, but symptoms remained higher in the progesterone than in the placebo group at the study's end.

There was no significant improvement in individual symptoms (eg, irritability) or clusters of symptoms (eg, "emotional" symptoms) between progesterone and placebo. There also was no difference between the two treatments in patients' overall reports of symptom severity, relief, and disruption of daily activity or in claimed from the NHLBI and the AHA.

### **BORDELIN HYPERTENSION LINKED WITH HIGHER CORONARY RISK**

Borderline hypertension, blood pressure levels above normal but below clear hypertension, is a predictor of atherosclerosis and has its roots in childhood, according to an article in the *Journal of the American Medical Association*.

"Borderline hypertension is neither transient nor inno-

cuous," write Stevo Julius, MD, ScD, from the Division of Hypertension, University of Michigan Hospitals, and colleagues. "Its association with other predictors of atherosclerosis calls for clinical attention."

Looking at 946 people aged 18 to 38 years in Tecumseh, Mich., the authors found that "subjects with borderline hypertension have a lifelong history of BP elevation," and that even with minimal elevation of blood pressure, they "exhibit early hypertensive changes in the heart and blood vessels."

The 822 people with normal blood pressure had measurements averaging 112 over 75, the study found. The 124 borderline hypertensive people had blood pressures averaging 131 over 94. The normal group had similar numbers of men and women; in the border line group, men outnumbered women three to one. None of the subjects were receiving antihypertensive treatment.

"A significant correlation between systolic BP and various risk factors was found across the whole range of BP distribution in Tecumseh," they write. "Much of this association is accounted for by subjects being overweight."

Subjects with borderline hypertension had higher heart rates, lower stroke volume, and significantly higher levels of plasma insulin, glucose, triglycerides, cholesterol concentrations and insulin-to-glucose ratios than the normal group.

While both groups were overweight according to Metropolitan Life Insurance tables, borderline subjects weighed an average of 13 kilograms more than the normal group. "After the effect of subjects' being overweight is statistically removed, the relationship of BP to risk factors ceases to be significant," the authors write.

The authors also found indicators of borderline hypertension in childhood. Data on many of the current subjects had been collected twice during the first decade of their lives. "Subjects who had borderline hypertension in the present study had significantly higher BP readings in their first decade of life than did subjects who were normotensive," they write. "This difference was further amplified at age 21."

The authors say their findings in Tecumseh "indicate that while borderline hypertension may be detected only in the fourth decade of life, the condition clearly has its roots in childhood. We also show that high BP readings in the fourth decade are part of a complex clinical picture that, in addition to slightly elevated BP, frequently includes elements of early cardiovascular structural changes and is associated with an increased risk for atherosclerosis... Hopefully, awareness that a subject with borderline hypertension has a high probability for abnormal atherosclerotic risk values will be translated into early management along the recommended national guidelines."

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### **MEDICARE REGULATIONS, OTHER RESTRICTIONS LIMIT HOSPICE CARE: REPORT**

Despite significant growth in the number of hospices in the U.S. during the past 15 years, changes in policies and

reimbursements are needed to provide more care to the dying, a report in the *Journal of the American Medical Association* concludes. Jill Rhymes, MD, of the Section of General Medicine, University of Chicago (Ill.) Medical Center, writes "most terminally ill patients are not cared for in hospices, and most physicians are not trained to provide terminal care." Dating back more than 2,000 years, the modern hospice movement began in 1967 in England. Limits imposed by Medicare, ignorance by many hospice executives and local pharmaceutical restrictions all conspire to reduce the numbers of hospice patients. It was predicted that 40,000 Americans would use Medicare benefits in hospices in 1985. Actually, only 13,000 patients did. Besides revamping governmental reimbursement methods, Rhymes writes that aspiring physicians need to be better educated in caring for the dying. "There is little education in pain control in most medical or nursing training," she writes. "Although some medical schools have developed programs in death and dying, most physicians and nurses have not been trained in caring for the terminally ill, and many are not comfortable in doing so."

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#### INTENSIVE CARE TREATMENT HELPS, NOT HURTS HOSPITALIZED ASTHMATICS: STUDY

The benefits of treating asthmatics in intensive care settings outweigh the disadvantages of using such a setting, according to a one-hospital study reported in the *Journal of the American Medical Association*. A decade's worth of hospitalized cases of status asthmaticus was studied by Sidney S. Braman, MD, and John T. Kaemmerlen, MD, of the Division of Pulmonary and Critical Care Medicine, Rhode Island Hospital and Brown University, Providence. The authors detected 80 cases in 64 patients during that time. Previous studies have noted that oversedation, undermedication and inadequate monitoring contributed to the deaths of hospitalized asthmatics. Fifty of the 80 cases studied at Rhode Island Hospital went to the intensive care unit because of a few complications. This was accomplished by close monitoring and repetitive blood gas analysis." The authors warned asthmatic patients who enter an emergency room with respiratory distress or failure and who continue suffer after vigorous therapy should be transferred to an intensive care unit immediately.

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#### BUNK BED INJURIES

During a one-year study, 68 children were injured falling from their bunk beds, and many of them were younger than the recommended age for sleeping in the double-decker beds, according to a study in June's *American Journal of Diseases of Children*. Steven M. Selbst, MD, Emergency Department, The Children's Hospital of Philadelphia, Penn., and his colleagues write that 70 percent of the injured children were younger than six years of age, which is below the age the Consumer Product Safety Commission says is safe for using bunk beds. In the vast majority of mishaps (94 percent), the beds were wood and 86 percent of them were stacked in the same direction. Surprisingly, less than one-third (29 percent) of the accidents occurred at night between 10 p.m. and 8 a.m. The majority of injuries resulted from a child falling from the top bunk, followed by ladder falls and hitting environment will help reduce some injuries," they conclude. "Also, since the law of gravity cannot be amended, the use of bunk beds should be.

#### PEAK AGE FOR ONSET OF SEVERAL MENTAL DISORDERS YOUNGER THAN PREVIOUSLY THOUGHT

Phobias, major depression, and alcohol and other drug dependence affect young men and women earlier in their lives than previously believed, according to research in June's *Archives of General Psychiatry*. Just a decade ago, researchers said major depression "may occur at any age, including infancy, and the age at onset is fairly evenly distributed throughout adult life." That position has changed significantly. Kimberly Christie Burke, MS, of the Office of the Director, National Institute of Mental Health, and her colleagues, report the median age for the onset of phobias—ranging from agoraphobia to social phobia—is 14 years in men and 13 years in women. Women suffer from anxiety disorders such as obsessive-compulsive and panic disorders more than men, according to the study of more than 2,000 subjects. The authors acknowledge the study was heavily weighted toward female subjects (73.5 percent) and they were more educated and had higher incomes than the general population. For panic disorders, the median age for onset was 24 years. The most important period when alcohol abuse and/or dependence affects young people occurs between 15 and 19 years of age.





# VASOTEC

## (ENALAPRIL MALEATE) (MSD)

VASOTEC is available in 2.5-mg, 5-mg, 10-mg, and 20-mg tablet strengths.

**Contraindications:** VASOTEC\* (Enalapril Maleate, MSO) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

**Warnings:** **Angioedema.** Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

**Hypotension.** Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Patients with heart failure given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy to continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy. (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hypotension, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS: Drug Interactions and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

**Neutropenia/Aggranulocytosis.** Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

**Precautions:** **General Impaired Renal Function.** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dose reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

**Evaluation of patients with hypertension or heart failure should always include assessment of renal function.** (See DOSAGE AND ADMINISTRATION.)

**Hyperkalemia.** Elevated serum potassium (>5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously if at all with VASOTEC. (See Drug Interactions.)

**Surgery/Anesthesia.** In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

### Information for Patients

**Angioedema.** Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

**Hypotension.** Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure. Patients should be advised to consult with the physician.

**Hyperkalemia.** Patients should be told not to use salt substitutes containing potassium without consulting their physician.

**Neutropenia.** Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

**NOTE:** As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

### Drug Interactions

**Hypotension.** Patients on Diuretic Therapy. Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

**Agents Causing Renin Release.** The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

**Other Cardiovascular Agents.** VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methylglucosides, calcium-channeling agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

**Agents Increasing Serum Potassium.** VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

**Lithium.** Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

**Pregnancy—Category C.** There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Following oral administration, fetotoxicity was observed in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters. There are no adequate and well-controlled studies of enalapril in pregnant women. However, data are available that

show enalapril crosses the human placenta. Because the risk of fetal toxicity with the use of ACE inhibitors has not been clearly defined, VASOTEC\* (Enalapril Maleate, MSO) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome: inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality.

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypotension, or the underlying prematurity.

**Nursing Mothers.** Milk in lactating rats contains radioactivity following administration of <sup>14</sup>C enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

**Pediatric Use.** Safety and effectiveness in children have not been established.

**Adverse Reactions:** VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

**HYPERTENSION.** The most frequent clinical adverse experiences in controlled trials were headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

**HEART FAILURE.** The most frequent clinical adverse experiences in both controlled and uncontrolled trials were dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

**Cardiovascular:** Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS: Hypotension); cardiac arrest, pulmonary embolism and infarction, rhythm disturbances, atrial fibrillation, palpitation.

**Digestive:** Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia, constipation, glossitis, stomatitis.

**Musculoskeletal:** Muscle cramps.

**Nervous/Psychiatric:** Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

**Urogenital:** Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

**Respiratory:** Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection.

**Skin:** Herpes zoster, urticaria, pruritus, alopecia, flushing, hyperhidrosis.

**Special Senses:** Blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

**Angioedema.** Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

**Hypotension.** In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

### Clinical Laboratory Test Findings

**Serum Electrolytes:** Hyperkalemia (see PRECAUTIONS); hyponatremia.

**Creatinine, Blood Urea Nitrogen.** In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

**Hemoglobin and Hematocrit.** Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

**Other (Causal Relationship Unknown).** In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported. A few cases of hemolysis have been reported in patients with G6PD deficiency.

**Liver Function Tests.** Elevations of liver enzymes and/or serum bilirubin have occurred.

**Dosage and Administration.** **Hypertension.** In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS: Drug Interactions.)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

**Dosage Adjustment in Hypertensive Patients with Renal Impairment.** The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine up to approximately 3 mg/dL). For patients with creatinine clearance < 30 mL/min (serum creatinine > 3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

**Heart Failure.** VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS: Drug Interactions.) If possible, the dose of the diuretic should be reduced, which may increase the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug. Following effective management of the hypotension, the usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study but nearly all patients in this study were given 40 mg the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV) patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY: Pharmacodynamics and Clinical Effects.) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

**Dosage Adjustment in Patients with Heart Failure and Renal Impairment or Hyponatremia.** In patients with heart failure who have hyponatremia (serum sodium < 130 mEq/L) or with serum creatinine > 1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION: Heart Failure, WARNINGS, and PRECAUTIONS: Drug Interactions.) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more. It is at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

For more detailed information, consult your MSD Representative or see Prescribing Information, Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19380.

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You do have to give up being afraid to take care of yourself.



Get a checkup. Life is worth it.



## Nuestra Portada

El escudo de la Universidad Central del Caribe, adoptado en el 1987, es de tipo inglés con escotadura en el borde superior central por donde proyecta la porción distal del báculo de Esculapio, primer médico de la mitología greco-romana, en el que se enrosca una serpiente, el antiguo símbolo de la salud. El báculo de Esculapio, termina como una antorcha con llama que *"es la antorcha de la esperanza que en el alma enciende su lumbr"*.

El cuadrante superior derecho representa la Sierra de Cayey recordando que la Universidad *"nace donde hay niebla en la cumbre"*.

El cuadrante superior izquierdo exhibe un microscopio alusivo a la investigación y en el inferior derecho se encuentra la tradicional lámpara con la luz del conocimiento que ha de superar la ignorancia: *"es donde se siembra la idea y florecen las inquietudes"*.

En el cuadrante inferior izquierdo se aprecia el maletín y el estetoscopio que por tantos años han distinguido a la figura del médico primario y de familia y que en el escudo representa a todos los egresados de todas las profesiones de la salud que se forman en la Universidad y que son responsables de que *"el futuro de nuestra tierra se reverdece en cosechas de juventudes"*.

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Rodea al escudo una franja circular con el nombre de la Universidad y la fecha de su fundación.

## FE DE ERRATA

En la edición de agosto 1990, en la página del Contenido aparece el artículo *Misreporting of Maternal Mortality in Puerto Rico*, página 343, fuera de lugar. Este artículo debe aparecer debajo del artículo *Primary Lateral Sclerosis: A Distinct Clinical Entity in Patients with Chronic Spastic Paraparesis*, página 340.

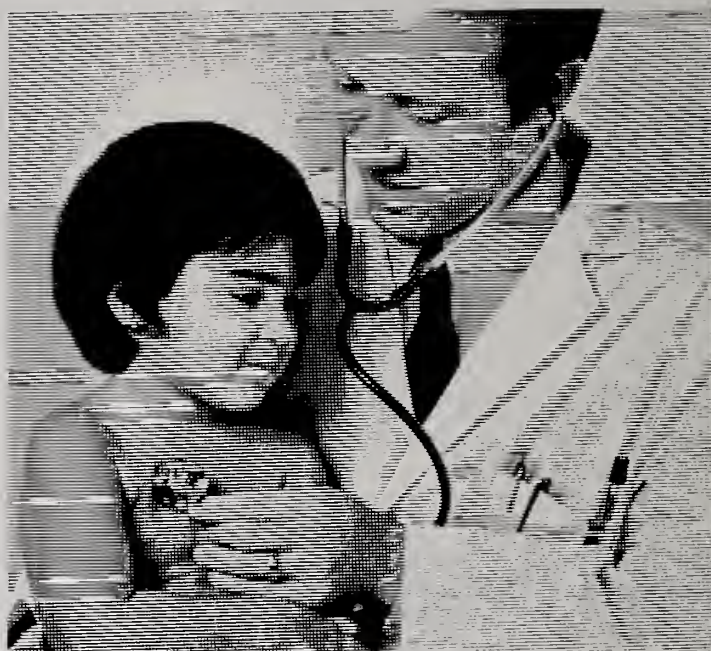
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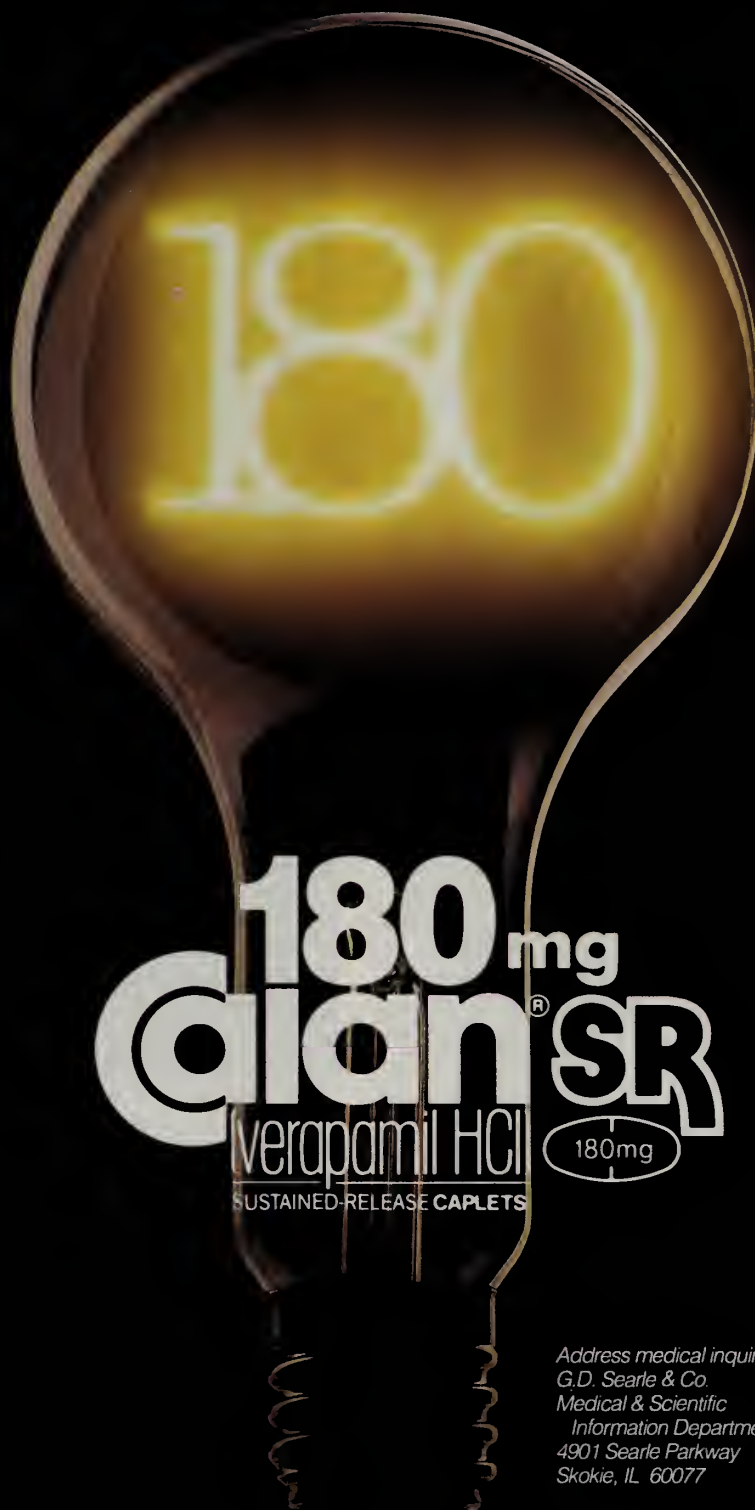
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# EDITORIAL



Este año se cumplen catorce años de la fundación de la Universidad Central del Caribe. A partir de este año de 1990, la Facultad de Medicina de la Universidad Central del Caribe asume la honrosa encomienda de responsabilizarse por el contenido científico y médico del número correspondiente al mes de septiembre de cada año del Boletín de la Asociación Médica de Puerto Rico. De esta manera, no solo proveemos un mecanismo adicional a nuestra facultad para diseminar el producto de su actividad erudita, sino que también contribuimos al desarrollo del Boletín de la Asociación Médica que tanto ha mejorado últimamente mediante el esfuerzo de su Junta Editora y, especialmente, de su diligente Editor, Dr. Rafael Villavicencio.

El compromiso ineludible de nuestra Universidad hacia el desarrollo pleno de un Centro Académico de las Ciencias de la Salud (Academic Health Center) en los terrenos del Hospital Universitario Ramón Ruíz Arnau en Bayamón, marcha con paso firme y férrea voluntad. Representa la meta de una institución, total y genuinamente de fines no pecuniarios, comprometida con el Pueblo de Puerto Rico en general y con la Región Noreste de Salud en especial: Bayamón, Cataño, Dorado, Toa Alta, Toa Baja, Vega Alta, Naranjito, Comerío, Barranquitas, Orocovis y Corozal. Once municipios con una población de alrededor de 700,000 habitantes. Dicho compromiso— de servicios al paciente, docencia pregrado y postgrado, tanto en medicina como en las demás profesiones relacionadas con la salud, y con la investigación básica y clínica— es uno que ha sido consistentemente avalado y respaldado por nuestro gobierno, prescindiendo de qué partido político se encuentre en determinado momento en el manejo de la cosa pública.

Algunas pruebas fehacientes del interés del Estado en el desarrollo de dicho Centro Académico de las Ciencias de la Salud bajo el liderato de la Universidad Central del Caribe son: (1) la Ley 125 de 1977 que autoriza a los departamentos, agencias e instrumentalidades del Estado a conceder bienes y servicios a las escuelas de medicina privadas debidamente acreditadas, (2) la Ley 103 de 1985 que exime a dichas escuelas de medicina privadas, debidamente acreditadas, de las obligaciones impuestas por dicha ley a toda entidad privada para poder contratar con el Departamento de Salud y AFASS por la utilización y operación de las facilidades médicas del Estado, (3) otorgamiento por el Gobierno de Puerto Rico a la Universidad Central del Caribe de los derechos de cesión de superficie en los predios del Hospital Universitario Ramón Ruíz Arnau, para la construcción del Edificio de Ciencias Biomédicas que se inaugurará el próximo noviembre a un costo aproximado de cinco millones de dólares y para las futuras expansiones que albergarán otras profesiones relacionadas con la salud, (4) en el

Discurso del Estado del País, el Gobernador de Puerto Rico en 1989, expresó como parte de su política pública en el área de la salud, las relaciones entre universidades y escuelas de medicina privadas con el Departamento de Salud y (5) la autorización por parte del Departamento de Salud y AFASS, desde el 1984, para retener los reembolsos generados de planes prepagados de salud por la facultad médica bajo contrato con la Universidad Central del Caribe para ser utilizados en el desarrollo de dicho Centro Académico. La Universidad invirtió en el Hospital Universitario Ramón Ruíz Arnau, durante el período entre julio de 1984 y diciembre de 1989, la cantidad de más de dos millones de dólares en la construcción de facilidades tales como la expansión del Departamento de Patología y Medicina de Laboratorio (microscopía electrónica, citología, inmunoquímica, fotografía e ilustración médica, microbiología especial y banco de sangre), la expansión del Departamento de Radiología, dotándole de un Centro de Imágenes de primera calidad, con tomografía computadorizada, dos unidades de ultrasonido y una unidad para mamografía, y la construcción de una clínica pediátrica con las más modernas facilidades. Además, se dotó al Hospital con múltiples salones de conferencia y unidades de oficina para cada jefe de departamento clínico.

El nuevo Edificio de Ciencias Biomédicas contará de una biblioteca con todas las facilidades modernas que garanticen a nuestra facultad médica y al cuerpo estudiantil la obtención de la más reciente y pertinente información biomédica en el período de tiempo más corto posible. También se dotará a dicho edificio con un bioterio o casa de animales que proveerá excelentes y muy amplias facilidades para la investigación biomédica y un laboratorio de cirugía experimental.

El Consejo de Educación Superior concedió recientemente la acreditación a nuestro programa de maestría en las ciencias preclínicas (Anatomía, Bioquímica, Fisiología, Microbiología y Farmacología) como primer paso en el desarrollo de nuestro Programa Graduado que esperamos en corto tiempo pueda ofrecer el grado de Doctor en Filosofía en las distintas ciencias preclínicas.

Confiamos en que el esfuerzo y el entusiasmo de nuestra facultad médica en cumplir con este compromiso para con el Boletín de la Asociación Médica de Puerto Rico y el producto de dicha gestión sean de vuestro agrado. De cualquier forma, nos sentimos honrados por la oportunidad que se nos ha brindado.

Raúl A. Marcial-Rojas, M.D., J.D.  
Presidente UCC y Decano de su  
Facultad de Medicina



# IN MEMORIAM

## **Raúl Armando Marcial Seoane, M.D.**

**"Su paso fue breve, su huella perenne"**



**N**ació nuestro querido Raulo el 29 de febrero de 1952, año bisiesto, quien sabe si como presagio a lo que fue "un ser humano muy especial, un amigo de todos, por su manera de ser una personalidad inigualable". Murió prematuramente el 13 de julio de 1990 víctima de un liposarcoma de los tejidos blandos del muslo izquierdo que se controló en su localización primaria, pero se metastatizó a distancia. Condición que aceptó con valentía y heroísmo y que nunca hizo desaparecer de su faz su sonrisa inigualable, amigable y bondadosa.

Su formación primaria y secundaria la obtuvo en el Colegio San Ignacio de Loyola. Siempre fue un

Ignaciano. Sus estudios de premédica los cursó en Mount Saint Mary's College en Emmitsburg, Maryland. Se graduó de médico en la Universidad de Puerto Rico en junio de 1977. Hizo un internado en patología (1977-78) y un año en radiología (1978-79) en la Universidad de Puerto Rico. Continuó sus estudios postgraduados en Radiología Diagnóstica por cuatro años adicionales (1979-83), incluyendo un "fellowship" en imágenes, en el Departamento de Radiología del Hospital de la Universidad Thomas Jefferson en Filadelfia. Era miembro diplomado del American Board of Radiology desde el 1983 y poseía licencia para ejercer su profesión de médico tanto en Pennsylvania como en Puerto Rico.

Pertenecía a las facultades médicas de la Universidad de Puerto Rico, del Centro Médico San Pablo y del Hospital Universitario Ramón Ruíz Arnau y la Universidad Central del Caribe. En estos últimos fue Director del Departamento de Radiología desde el 1985, y logró un programa afiliado a la residencia de la Universidad de Puerto Rico. Diseñó, fundó y operó el Centro de Imágenes hasta casi el momento de su muerte. Tuvo la enorme satisfacción de conocer en vida de la Resolución de la Facultad de Medicina de la Universidad Central del Caribe y del Hospital Ramón Ruíz Arnau que solicitaba de las Juntas de Gobierno de ambas instituciones que se designara dicha nueva facilidad como el Centro de Imágenes Dr. Raúl A. Marcial-Seoane.

Pertenecía a la Asociación Médica de Puerto Rico y a su Sección de Radiología, así como al American College of Radiology y a la Sociedad de Gastroenterología de Puerto Rico. Había escrito varios trabajos médicos entre los cuales están dos que se publican en este número del Boletín de la Asociación Médica de Puerto Rico.

Fue siempre un gran deportista. Sus deportes favoritos eran el polo acuático, el tennis y la natación. Formó parte del Equipo Nacional de Polo Acuático de Puerto Rico en los Juegos Centroamericanos y del Caribe en Panamá (1970) y en los Juegos Panamericanos en Cali, Colombia (1971).

Le sobreviven su viuda Margarita y sus hijos Raúl Vicente (12), Jorge Armando (9) y José Manuel (6), así como sus padres Alodia y Raúl, sus hermanos Alodia, Ana Rosa y Manuel y ocho sobrinos.

La muerte prematura del doctor Raúl A. Marcial-Seoane no solo privó a Puerto Rico de un excelente profesional médico en el campo de la radiología, sino también a todos los que le conocíamos de un gran ser humano. Descanse en paz.

Tus amigos y compañeros.

# Oncology Review

## Bone Tumors of Mixed Origin: Osteo-Liposarcoma and Osteo-Rhabdomyosarcoma\*

+ Raúl A. Marcial-Seoane, MD  
Manuel A. Marcial-Seoane, MD  
Francisco J. Dávila-Toro, MD  
Raúl A. Marcial-Rojas, MD, JD

The annual incidence of malignant tumors of bone is approximately one case per 100,000 inhabitants.<sup>1</sup> This infrequent occurrence of malignant bone tumors justifies reporting in the literature single or small group of cases, especially of the most unusual tumors, in order to learn more about their diagnosis, treatment and prognosis.

Among all malignant tumors, less than 1% of them are primary sarcomas of bone.<sup>2</sup> In this article we will be dealing with the following neoplastic nosologic entities of bone: (a) primary liposarcoma, (b) primary rhabdomyosarcoma, (c) primary malignant mesenchymoma (osteoliposarcoma and osteo-rhabdomyosarcoma) and (d) "dedifferentiated" chondrosarcoma.

To emphasize the extreme infrequency of some of the above mentioned primary neoplastic lesions of bone, suffice it to say that among the 8,542 primary benign and malignant tumors of bone seen at the Mayo Clinic, only one case of primary liposarcoma is included and no cases of either primary rhabdomyosarcoma or malignant mesenchymoma of bone have been seen.<sup>3</sup>

### Primary Liposarcoma of Bone

The infrequency of primary liposarcoma of bone, the relative frequency of its counterpart in the soft tissues, the great variability in the histologic appearance of liposarcomas, and the frequency of metastasis to bone from all types of malignant tumors with varying histology, including liposarcoma of the soft tissues, are factors to be carefully considered and analyzed before rendering a diagnosis of primary liposarcoma of bone.

Tumors of adipose tissue are of common occurrence in the soft tissues. Liposarcoma is one of the most common of the adult soft-tissue sarcomas, with a reported incidence that varies from 10% to 25% of all soft tissue sarcomas.<sup>4</sup>

The following two criteria must be met before accep-

ting a particular case as a bona fide primary liposarcoma of bone: (1) microscopically the tumor must fit into any of the variable histologic pictures of liposarcoma and (2) clinically, radiologically and macroscopically one must prove, with reasonable certainty, that the tumor arose within the medullary cavity and that it neither represents an extension from the adjacent parosteal soft tissues nor a metastasis to bone.

Needless to say that primary liposarcoma of bone, like any other primary bone sarcoma, may erode, invade and penetrate the cortex, producing a parosteal mass. In these cases, the radiologic and macroscopic pictures are extremely helpful, and seldom leave any reasonable doubt about the exact origin of the tumor. The pattern of cortical destruction from inside outwards, the elevation of the periosteum with the possible formation of subperiosteal reactions, like the so-called Codman's triangle or a well-developed buttress, and the occasional permeative pattern of cortical invasion are features which characterize primary lesions of bone.

It is also important to emphasize that liposarcomas of soft tissues adjacent to bone seldom invade the cortex, less penetrate into the medullary cavity. A study by Brasfield and Das Gupta (1970)<sup>5</sup> of 236 soft tissue liposarcomas disclosed 18 cases with bone involvement. Wilner<sup>6</sup> reviewed the roentgenograms in these cases and noted that in 15 instances, the bony changes were confined to the cortex. There was evidence of wavy erosive changes, cortical thickening, cortical destruction or localized, cortical or parosteal, bony overgrowth. Only three patients in this series exhibited invasion of tumor in the medullary cavity.

In 1966 Reszel, Soule and Coventry<sup>7</sup> reported 222 cases of liposarcoma of the soft tissues of the limbs and of the scapulo-humeral and pelvic girdles and did not find one single case with extension of bone.

Liposarcomas of the soft tissues, however, not infrequently metastasize to the bone marrow. In some series, this is the most frequent site of metastasis after lungs and liver.<sup>8</sup> The presence of a primary liposarcoma in the soft tissues and the clinical picture of multiple bone metastasis definitely exclude the possibility of a primary liposarcoma of bone.

The existence of primary liposarcoma of bone was noted by Ewing at the London Cancer Congress of 1928.<sup>9</sup>

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†Died July 13, 1990

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In 1931 Stewart<sup>10</sup> reported in detail 3 cases from Memorial Hospital, 2 of which had formed the basis for Ewing's tentative recognition of the disease.<sup>9</sup> Stewart<sup>10</sup> cautiously interpreted those 3 cases as primary liposarcoma of bone. It is our opinion, after careful study of the clinical history, gross and microscopic photographs and outcome of these three cases, that Cases 1 and 2 do not fulfill the criteria for the diagnosis of primary liposarcoma of bone. Only Case 3, in our opinion, could fulfill said criteria.

During the next seven years another five (5) cases of liposarcoma of bone were described: Fender (1933)<sup>11</sup>, Barnard (1934),<sup>12</sup> two by Rehbock and Hauser (1936)<sup>13</sup> and Duffy and Stewart (1938).<sup>14</sup> The authors conclude that some of these cases are difficult to accept and have been previously criticized because of inadequate or unconvincing clinical or pathologic data. In the case reported by Fender<sup>11</sup> no evidence was presented that the primary tumor developed inside the bone (fibula). The two cases of Rehbock and Hauser<sup>13</sup> cannot be accepted by us, the first because of the marked delay in radiography and the second because of the large retroperitoneal mass, a frequent site for liposarcoma, extending to sacrum and probably ilium.

Dawson (1955),<sup>15</sup> Fialho and Barcellos (1958),<sup>16</sup> Cohen (1958),<sup>17</sup> Coste, Lapresle and Basset (1959),<sup>18</sup> Mastragostino (1957),<sup>19</sup> Retz (1961),<sup>20</sup> Catto and Stevens (1963),<sup>21</sup> Honore, Rogister and Delvigne-Vanlacker (1963),<sup>22</sup> and Goldman<sup>23</sup> added nine additional reports to the literature. Only the cases of Catto and Stevens,<sup>21</sup> Dawson,<sup>15</sup> Goldman,<sup>23</sup> Honore<sup>22</sup> and Mastragostino<sup>19</sup> were considered completely convincing according to Lichtenstein.<sup>24</sup>

Johnson, Vetter and Putschar (1962)<sup>25</sup> in their article reporting sarcomas arising in bone cysts mentioned two cases which could represent liposarcomas of bone.

Thirteen more cases have been reported since 1970,<sup>26-35</sup> of these, the following three cases are not acceptable to us as convincing primary liposarcomas of bone: (1) the case reported by Agarwall and associates<sup>28</sup> as primary in the mastoid of a 4-year old boy, because of the age (4 years), clinical presentation as a purulent mastoiditis with otorrhea, inadequate radiographic and pathologic descriptions and immediate post-operative death with lack of a postmortem examination; (2) the primary liposarcoma of the skull reported by Srivastava et al<sup>29</sup> stated that the radiographs "showed areas of bone destruction and bone formation" and "bone formation within the soft tissue" adjacent to the tumor. The microscopic description is extremely inadequate and there is only one microphotograph published and no histologic description of the areas of bone formation to be able to determine if it was reactive or neoplastic. In the latter situation the case fits better the diagnosis of malignant mesenchymoma of the osteo-liposarcoma type which we will describe later. There was no adequate follow-up after the initial excellent response to radiotherapy. The third case, that of Schneider and collaborators<sup>32</sup>, is most certainly an osteo-liposarcoma, as the tumor is described as "partly soft and partly of osseous structure". Despite of the fact that they claim that "osteoid formations belonging to the tumor are not visible", one cannot completely accept this case as

a pure liposarcoma. Further on in this article we will elaborate about the fact that "the majority of the authors, interested in proving the authenticity of the osseous origin and the liposarcomatous character of the tumors they were studying, did not give their attention to the probable existence of another cellular type besides the lipomatous one in different degrees of maturity and differentiation".<sup>36</sup>

Torok et al (1983)<sup>35</sup> reported a case and reviewed the literature on primary liposarcoma of bone from 1930-1980 and found "20 papers describing about 30 isolated cases".

After careful analysis and evaluation of the reported cases with adequate radiologic and pathologic descriptions, it is our opinion, that not more than twenty cases fulfill all the essential criteria for the diagnosis of bona fide primary liposarcoma of bone. These twenty cases, contrary to Torok's statement<sup>35</sup> that the lesion did not show sex predilection, disclosed a male predominance: 15 male to 5 female with a 3 to 1 male-female ratio. The age distribution and the exact bone involved in these twenty cases are depicted in Tables I and II. Most cases occur between the ages of 25-45 years. It is not possible, with the information available, to determine exactly if there is a preference for a specific region of the particular bone affected. Most of the tumors are described to be located in the shaft or in the metaphysis.

As far as prognosis is concerned, thirteen of the twenty cases were dead between one to three years after the original diagnosis, primarily with metastatic disease to the lungs. For the seven cases surviving, at the time of the original report, the follow-up was too short. Dominok et al<sup>37</sup>

Table I

Primary Liposarcoma of Bone Age Distribution	
16-20 years	3 cases
21-30 years	3 cases
31-40 years	7 cases
41-50 years	4 cases
51-60 years	2 cases
61-70 years	0 cases
71-80 years	1 cases
	20 cases

Table II

Primary Liposarcoma of Bone Bone Involved	
Femur	6 cases
Tibia	6 cases
Humerus	5 cases
Fibula	2 cases
Ulna	1 cases
	20 cases

reported in 1977 the death of 80% of the 28 patients with primary osseous liposarcoma reviewed from the literature, after 2 years, because of metastases. There is not enough experience, due to the rare occurrence of this tumor, as to its response to chemotherapy. We know that it is radiosensitive but how radiocurable it is cannot at present be ascertained. These patients, usually, are locally controlled of their primary tumor, either by surgery or radiotherapy, or a combination of both; however, the frequent cause of therapeutic failure and death is metastatic disease.

### Primary Malignant Mesenchymoma of Bone

The lesion known as primary malignant mesenchymoma of bone was first reported by Schajowicz et al<sup>36</sup> in 1966. It was considered to be a new tumor entity in bone. As stated in said case report<sup>36</sup>, the original biopsy disclosed a histologic picture of liposarcoma; however, when the amputation specimen of the tibia was studied, besides its liposarcomatous predominance, "large areas with all the macro and microscopic characteristics of an osteogenic sarcoma (osteosarcoma), without clearly defined limits between the two neoplastic types"<sup>36</sup>, were evident.

Stout<sup>38</sup>, in 1948, although he was not the first to coin the term "mesenchymoma", he advocated that it be confined to a group of rare tumors, benign and malignant, that arise from two or more elements of mesenchyme, not including fibrous tissue. These tumors, composed of at least two unrelated types—vascular, adipose, muscular (smooth or striated), bone, cartilage, etc.—have been found in practically all areas of the body. The exclusion of the fibrous component is accounted for the fact that a fibrosarcomatous-like component can form part of any tumor of mesenchymal origin.

Schajowicz<sup>36</sup> classified their case as a primary malignant mesenchymoma of bone, composed of malignant osseous and lipomatous derivatives. Ross and Hadfield<sup>39</sup> in 1968 reported a similar tumor of the fibula in a fifteen year old boy and utilized for the first time in the literature the term *primary osteo-liposarcoma* of bone, implying it represented a specific type of primary malignant mesenchymoma of bone. The authors are of the opinion that, for reasons to be elaborated below, the term primary osteo-liposarcoma of bone should be retained as the best and most descriptive for this entity.

Kipkie and Haust in 1959<sup>40</sup> reported a malignant mesenchymoma of the mandible in a five-year old of the hemangioblastomyxomatous variety. It is of interest that the latter report was published seven years before Schajowicz et al<sup>36</sup> proclamation of malignant mesenchymoma as a new tumor entity. In 1969 Sterns, Haust and Wollin<sup>41</sup> reported another malignant mesenchymoma of the mandible, in a 15-year old boy, of the angiomatous, primitive mesenchymal and cartilagenous types of components. This patient died, mostly of pulmonary metastases, eighteen months after the initial diagnosis and following radiotherapy, surgical resection and chemotherapy.

In 1978 Bertoni and Laus<sup>42</sup> reported a primary malignant mesenchymoma of the proximal metaphysis of the right tibia in a fifteen-year old boy. The diagnosis

in the biopsy was classical of pleomorphic liposarcoma; however, when the amputated specimen was carefully studied, it disclosed areas of osteosarcoma.

In June 1990, Scheele et al<sup>43</sup> reported a primary malignant mesenchymoma of bone in the right acetabulum of a 69-year old white man. The tumor extended to the soft tissues and was composed of "three distinct components: rhabdomyosarcoma, chondrosarcoma and osteosarcoma."<sup>43</sup> We are convinced that Scheele's case<sup>43</sup> is not a primary malignant mesenchymoma of bone and for practical purpose should be included in the group of dedifferentiated chondrosarcomas with additional malignant mesenchymal components. We will elaborate further about this case in the section of dedifferentiated chondrosarcomas with additional mesenchymal component.

We have not been able to find in the literature any other case reported as primary malignant mesenchymoma of bone, and only five cases of primary osteoliposarcoma of bone have been reported after the single cases of Schajowicz<sup>36</sup>, Ross<sup>39</sup>, and Bertoni.<sup>42</sup>

Some reflections are in order pertaining to the term malignant mesenchymoma of bone. It is not unusual for osteogenic sarcomas to present chondrosarcomatous or fibrosarcomatous areas and still retain the diagnosis of osteogenic sarcoma, as well as its prognosis which is not significantly altered. In other words, it is a well accepted fact that the primitive mesenchymal cell in bone can and frequently does differentiate along fibroblastic, chondroblastic and osteoblastic lines of specialization.

Hutter et al<sup>44</sup> described a small group of bone tumors not readily classified in any single category since each one had histologic components of more than one major type of primitive sarcoma of bone. They<sup>44</sup> designated these rare tumors as *primitive multipotential primary sarcomas of bone*; "primitive because each appears to have a common type of undifferentiated cell; *multipotential* because each shows differentiation along multiple lines (i.e. bone, cartilage, blood vessels, etc.); *primary* to emphasize the fact that, although some of these tumors may have areas that histologically mimic metastatic lesions such as adenocarcinoma or neuroblastoma, they are truly primary in bone."<sup>44</sup> It is of interest that the distribution of the twenty-five cases then presented was rather unusual, as twelve were located in the long tubular bones but thirteen in short and flat bones, including bones of the face, of which three were in the maxilla.

Johnson (1952)<sup>45</sup>, while presenting his general theory of bone tumors to the New York Pathological Society, clearly postulated that the variations in how tumors duplicated the interstitial components (cartilage, bone, collagen) of specific types of matrix depended primarily on the metabolic milieu in which the tumor arose than on the specific cell of origin. Bassett<sup>46</sup> stated that the resources within its environment influence the type of products that the cell can synthesize and deposit, in spite of the fact that the cell has a definite genetic determination. Thus further support is granted to the importance of the metabolic field over the specific cell.

Many of the tumors differentiating to chondroid or cartilage, and alternating with other areas of vascular or hemangiopericytoid structures, described by Hutter,<sup>44</sup> were previously described as *mesenchymal chondro-*



sarcomas by Lichteinstein and Bernstein in 1956<sup>47</sup> and Dahlin and Henderson in 1962.<sup>48</sup> This entity was further substantiated with a report of 30 new cases, bringing the total of documented cases, in skeletal and extraskeletal sites, to only 51.<sup>49</sup> It is significant to emphasize that the ribs and the jaws are the most frequent skeletal sites of this tumor.

From the above information, and from the histologic description and clinical course of the malignant mesenchymoma of the mandible reported by Sterns et al,<sup>41</sup> we must conclude with reasonable certainty that said tumor was a mesenchymal chondrosarcoma and should not be diagnosed as malignant mesenchymoma.

Jacobson in 1977 coined the term *polyhistioma*, defining it as "a sarcoma of small round cells with isomorphic nuclei and scanty cytoplasm, which differentiates into one or more mesodermal tissues".<sup>50</sup> He included in this definition all the primitive multipotential primary tumors reported by Hutter,<sup>44</sup> no matter if they presented the known histologic picture of mesenchymal chondrosarcomas of skeletal and extraskeletal sites previously reported. We cannot support mixing back into a pool of variable, undifferentiated tumors, an entity like mesenchymal chondrosarcoma of the soft or skeletal tissues, which can be identified histologically with a reasonable degree of certainty. Keeping this entity as a group will continue to permit elaborating a reasonable experience as to the clinical diagnosis and evolution, treatment and prognosis of mesenchymal chondrosarcomas. There is no disagreement on our part that all polyhistiomas are not mesenchymal chondrosarcomas, but those which fulfill their criteria for diagnosis we should continue to recover from the unfenced field of polyhistiomas, as mesenchymal chondrosarcomas.

We agree wholeheartedly with Jacobson<sup>50</sup> when he states that "this tumor (polyhistioma) should not be confused with the rare entities in which more than one tissue becomes neoplastic". Also when he claims: "Polyhistioma is not a mesenchymoma."<sup>50</sup>

At present we propose that the term coined by Schajowicz<sup>36</sup> of primary malignant mesenchymoma of bone be abandoned and substituted by the combined name of the neoplastic tissues forming said tumors, under the classification of Tumors of Mixed Origin. This communication will present the ninth reported case of *osteoliposarcoma* and the first of *osteorhabdomyosarcoma*.

### Primary Osteoliposarcoma of Bone

The facts, well established in the literature, are that Schajowicz et al<sup>36</sup> were the first to describe this lesion as a primary malignant mesenchymoma of bone, composed of liposarcomatous and osteosarcomatous tissues. Ross and Hadfield<sup>39</sup> were the first to coin our preferred term of osteoliposarcoma. As such it was classified, under "Tumors of Mixed Origin", in the Atlas of Tumor Pathology published by the Armed Forces Institute of Pathology in 1971.<sup>51</sup> In the International Histological Classification of Tumors of the World Health in 1972<sup>52</sup> it is classified under "Other Connective Tissue Tumors" as Malignant Mesenchymoma. In said classification (p. 43) this tumor is defined as "characterized by the presence of

multiple types of differentiation and structural pattern, particularly those not usually encountered in the skeleton". It also stated that this tumor "is an exceedingly rare type of tumour and needs further study. The few reported cases show a combination of osteosarcomatous and liposarcomatous components". The authors favor keeping this tumor under the specific name of osteo-liposarcoma, either under the "Tumors of Mixed Origin"<sup>51</sup> or under "Other Connective Tissue Tumors as Malignant Mesenchymoma".<sup>52</sup>

These facts do not necessarily mean that this lesion was previously non-existent. Schajowicz<sup>36</sup> clearly states that several of the previously reported cases of primary liposarcoma of bone were in all probability osteoliposarcomas, as the radiographs disclosed a biphasic pattern and bone formation was most likely neoplastic. This has also been the experience during our present review of the literature of primary liposarcoma of bone. The most obvious case, where the osteosarcomatous element was not reported, and the lesion was published in 1980 as a primary liposarcoma of bone, is that of Schneider et al.<sup>32</sup> In this case the biphasic radiologic picture composed by multiple radiopaque and radiolucent areas in the fibula; the gross description of the tumor as partly soft and partly of osseous structure and the microscopic presence of new bone formation, although interpreted by the authors as non-neoplastic, all are clear evidence of a mixed tumor of osteoliposarcoma type. This is further substantiated by the abundant extracellular ground substance, described by the authors as dense collagen which most probably represents osteoid. For the purpose of our review of the literature, we will consider this tumor reported by Schneider<sup>32</sup> as an osteoliposarcoma. We will disregard other questionable cases reported as primary liposarcomas of bone which could have represented osteoliposarcomas and limit our review of the literature to those tumors specifically described as osteo-liposarcomas. (Table III)

Eight cases of osteoliposarcoma of bone,<sup>36, 39, 42, 53, 54, 55</sup> including Schneider's,<sup>32</sup> have been recovered from the world literature and a ninth case is hereby reported by the authors.

Osteoliposarcoma shows a marked preference for the long bones of the lower extremity. Eight of the nine cases were localized in the tibia,<sup>4</sup> femur<sup>2</sup> and fibula.<sup>2</sup> (Table III)

The few cases of osteo-liposarcoma reported do not permit a significant evaluation as to the age and sex distribution of this tumor entity. Five cases occurred in men, three in women and in one case the sex is not recorded. As far as the age distribution there were four cases in the second decade, and one in each of the 4th, 5th, 6th and 7th decades. Six of the nine cases (in one the age was not recorded) were in the ages of 10 to 41 years (Table III). The case in which the sex and age were not recorded is the one reported by Lichteinstein in his book.<sup>53</sup>

The sample is so limited in number that an attempt to evaluate therapy is worthless. Besides, chemotherapy was either not available or in its early years. Seven cases were treated by amputation. Radiotherapy and chemotherapy alone were given to the lesions of the ileum and to one of the fibula cases. There was metastases recorded in five cases. In one case there was no follow-up,<sup>36</sup> another was

Table III

Primary Osteoliposarcoma of Bone						
Date	Author	Age	Sex	Site	Metastases	Survival
1966	Schajowicz et al	17	M	Tibia	N.R.	N.R.
1968	Ross et al	15	M	Fibula	Lung	9 months
1977	Lichtenstein	N.R.	N.R.	Tibia	Lung and Mediastinum	
1978	Bertoni et al	15	M	Tibia	None	Lost to follow-up after 3 months
*1980	Schneider et al	69	M	Fibula	None	Lost to follow-
1981	Cremer et al	58	F	Femur	Lung	2.5 years
1981	Cremer et al	37	F	Ileum	Brain	3 years
1988	Bosman et al	10	F	Femur	Lung	12 months
1990	Marcial-Seoane et al	41	M	Tibia	None	Alive 20 years

N.R. Means not recorded.

\*This case was originally reported in the literature as primary liposarcoma of bone. See text of article.

published only three months after amputation<sup>42</sup> and a third case was lost to follow-up after two years.<sup>32</sup> Our case is alive and free of disease twenty years after amputation.

### Case Report

A 41-year old man, with a history of trauma to the proximal portion of the left leg five years before, who developed a swelling below the right knee. The swelling increased in size during the year prior to admission and became slightly painful.

Radiographs disclose a primarily osteolytic geographic lesion with well defined margins. The latter are slightly sclerotic in areas. The lesion is centrally located in the medullary cavity and occupying the uppermost portions of the proximal third of the shaft of the tibia and extending to the proximal metaphysis. There are some small areas of bone matrix formation within the lesion. The endosteum is slightly thickened in areas (Fig. 1). There is an area of complete cortical destruction, in the most proximal portion of the lesion, appearing as a markedly radiolucent window affecting the cortex in both sides of the bone. The radiolucent window is surrounded by well defined slightly sclerotic margins (Fig. 2). The area of the paraosteal swelling is at the level of the cortical radiolucent window.

A biopsy was performed of the paraosteal soft tissue mass protruding through the destroyed cortex. The tissue was grossly characteristic of lipomatous neoplastic tissue. A frozen-section disclosed a rather pleomorphic liposarcoma of bone. An above the knee amputation was performed.

The tibia disclosed the presence of a neoplasm destroying the medullary canal of the proximal shaft and with extension to the proximal metaphysis. The tumor tissue was yellowish and disclosing hemorrhagic areas. There was cortical destruction evident in the medial and lateral aspects of the upper tibia, with tumor tissue extending outside, but still contained within the periosteum. Some



Figure 1. Geographic lesion in proximal third of tibia extending to proximal metaphysis. Endosteum is slightly thickened in areas and there are small areas of bone matrix formation.





Figure 2. Prominent radiolucent area due to liposarcomatous component with through and through cortical destruction.



Figure 3-A. View of the halves of the bisected specimen of the tibia after all normal soft tissues were removed. Notice the destructive lesion of upper third, extending to proximal metaphysis. Also the tumor extension through the destroyed cortex.



Figure 3-B. Radiographs of bisected halves shown in A. The through and through radiolucent window produced by tumor cortical destruction is evident. Areas of mineralized osteogenic matrix are evident in the medullary portion of the tumor.

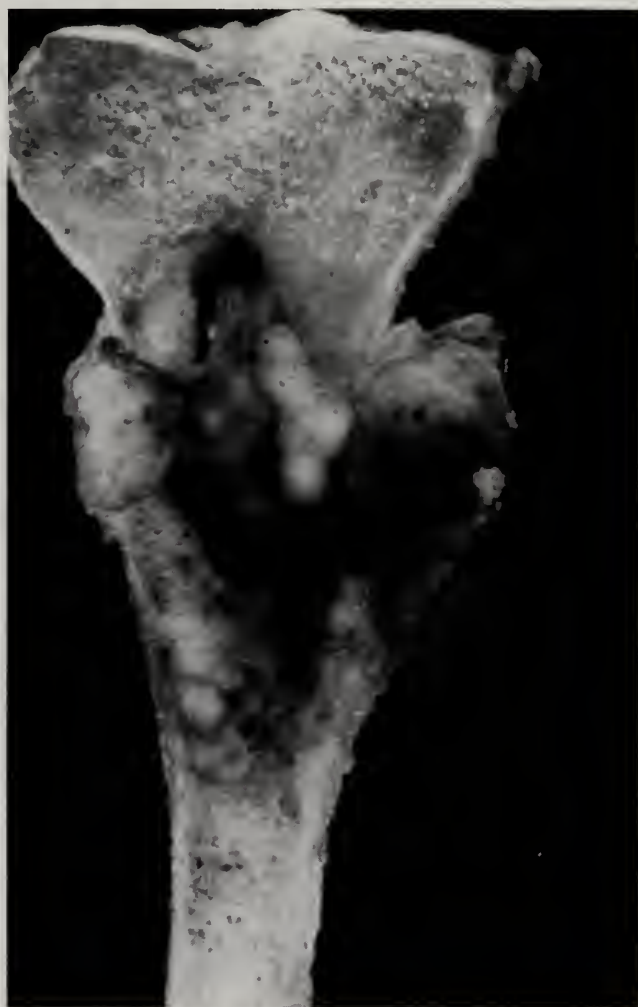


Figure 3-C. Close up view of tumor after bissection. Notice the hemorrhagic liposarcomatous areas and the discrete osteosarcomatous nodules. The tumor destroys the cortex but is still confined by periosteum.

grayish-white areas were evident within the tumor. These were firm and slightly gritty, obviously representing the osteogenic component (Fig. 3).

Histologic sections in most areas exhibited the classical appearance of a pleomorphic liposarcoma with tumor giant cells disclosing prominent multilobulated nuclei

(Fig. 4A and B). Some of the cells presented prominent vacuoles which were positive for fat in special stains (Fig. 5A and B). Sections from the grayish and firm areas exhibited tumor cells with intervening osteoid characteristic of osteogenic sarcoma (Fig. 6A and B).

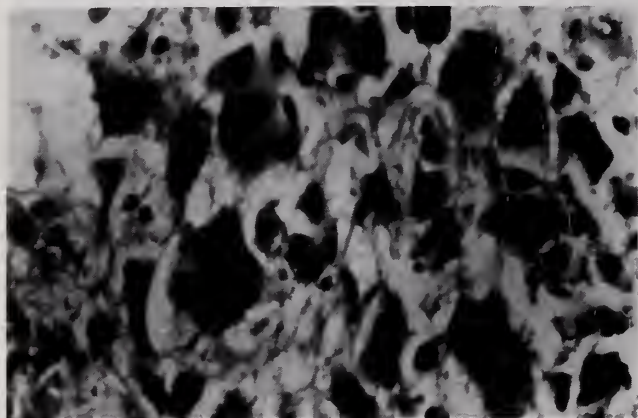


Figure 4-A. Areas of pleomorphic liposarcoma depicting giant tumor cells with multilobulated nuclei.

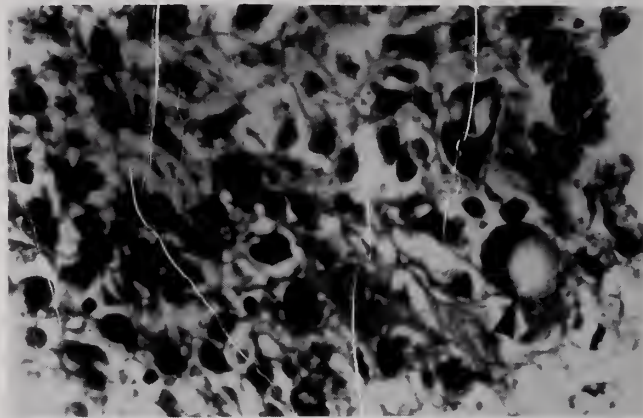


Figure 5-B. Higher magnification disclosing malignant lipoblast with prominent vacuolization (arrowhead).

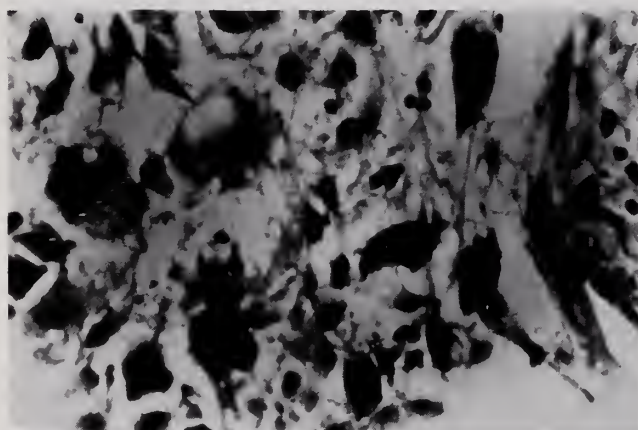


Figure 4-B. Prominent vacuole in large malignant lipoblast marked by arrow.



Figure 6-A. Osteoid matrix is clearly evident in the osteosarcomatous areas of the osteoliposarcoma.

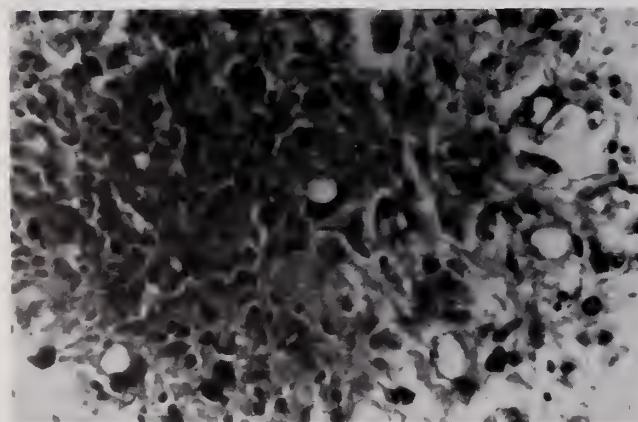


Figure 5-A. Numerous vacuolated malignant lipoblasts are evident. Special stains for fat were markedly positive.

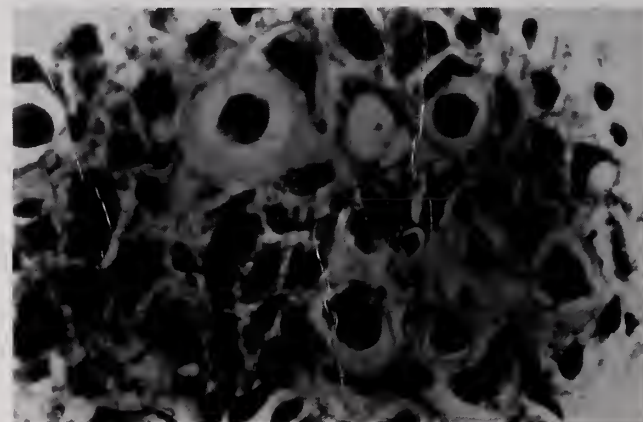


Figure 6-B. Higher magnification of the neoplastic osteoid forming areas.



### Primary Rhabdomyosarcoma of Bone

Pasquel et al (1976)<sup>56</sup> reported, what they considered to be a primary rhabdomyosarcoma of bone, in the midshaft of the femur of a 13-year old girl. The clinical and radiological diagnosis originally entertained was osteogenic sarcoma. A first incisional biopsy revealed osteoblastic proliferation which was interpreted as new-bone formation consistent with reactive callus formation. A second biopsy, eight days later, disclosed what was diagnosed as a fully differentiated embryonal rhabdomyosarcoma primary in bone. There were cross striations in some of the tumor cells. Cobalt radiotherapy (7,000 rads) and chemotherapy (actinomycin D and vincristine) were administered when the patient's family refused amputation. There was apparently no significant improvement and a coxofemoral disarticulation was performed. A chest roentgenogram, eight months after initiation of therapy, revealed a metastatic lesion in the left lung base.

Since the authors of this article saw Pasquel's report, specifically the photographs of the two radiographs of the femur, we could not help but suspect that the tumor was not a pure rhabdomyosarcoma, as Fig. 1<sup>56</sup> (before fracture) disclosed an area of productive bony changes in the midportion of the medullary lesion. However, there is no doubt that we are dealing with a primary tumor of bone.

The suspicion that this case, in all reasonable certainty, represented a very rare tumor of bone of the mixed origin variety, with the combination of osteosarcomatous and rhabdomyosarcomatous elements, was entertained; as the senior author (RAMR) had seen a similar case in a 12-year old girl in 1972. The latter case is subject of the present report.

The case reported by Pasquel et al<sup>56</sup> in 1976 was contributed to and published by Wilner<sup>57</sup> in his authoritative treatise on bone tumors and allied disorders. Wilner<sup>57</sup> published it as a primary rhabdomyosarcoma of bone as "according to Pasquel only one tissue component could be identified in the tumor". However, it is obvious that the descriptions of the radiologic picture of this tumor in the two respective publications are remarkably different. In the original article (Figures 1 and 2),<sup>56</sup> the only reference to the formation of osseous matrix was that of periosteal reaction. In Wilner's text (Figures 44-3, A and B),<sup>57</sup> the biphasic nature of the lesion is excellently depicted and described. In addition to the presence of some laminated periosteal new bone formation in the roentgenogram taken at the onset of symptoms, productive bony changes are also described in the midportion of the lesion (Fig. 44-3-A).<sup>57</sup> In the radiograph taken about two weeks after pathologic fracture (Fig. 44-3-B), Wilner<sup>57</sup> states: "Note the dense, oval area of sclerotic bone in the midportion of the lesion and the surrounding periosteal new bone formation in the femoral shaft." We cannot reconcile this radiologic picture<sup>57</sup> with the original pathological description,<sup>56</sup> both gross and microscopic, where there is no mention of neoplastic bone within the medullary lesion. It is true that the specimen was amputated after receiving 7,000 rads, but the authors of the article<sup>56</sup> stated that "tumor was

well preserved and appeared viable despite the radiotherapy and chemotherapy". However, they postulated the presence of "moderate radiation changes, such as cellular pleomorphism, vacuole formation in the cytoplasm and stromal hyalinization". We feel certain to postulate that the latter was probably osteoid with radiation effect. One is forced to conclude that the amputated specimen in this case was not adequately surveyed, as if enough representative sections would have been taken an osteosarcomatous component should have been evident. Our conclusion is that Pasquel's case<sup>56</sup> is not a pure primary rhabdomyosarcoma of bone and that it represents a primary mixed tumor of osteogenic and striated muscle components: an *osteo-rhabdomyosarcoma*. If one prefers the WHO Classification it should be classified under Malignant Mesenchymoma of Bone.<sup>52</sup>

In 1986, Hsueh et al<sup>58</sup> reported what they considered to be the second documented case of primary rhabdomyosarcoma of bone. The first was supposed to be the one reported by Pasquel et al<sup>56</sup>, which we have previously discussed.

The patient reported by Hsueh et al<sup>58</sup> was an 11-year old boy with a primary malignant lesion of the distal metaphysis of the right femur, extending across the growth plate into the epiphysis. He presented with a progressively enlarging and painful mass. The clinical and radiologic impression was that of osteogenic sarcoma. As in Pasquel's case,<sup>56</sup> the histologic component which mostly impressed the authors was the extremely rare rhabdomyosarcomatous one. They claimed<sup>58</sup> that "reaction bone formation" was observed, "but no malignant osteoid was found". We can not help but to consider this case, as Pasquel's one,<sup>56</sup> similar to the one which is reported in this article as an osteo-rhabdomyosarcoma. In our case, only after careful and extensive evaluation of the whole specimen were the typical areas of osteosarcoma disclosed. We realized that such an interesting case urges for a prompt publication, but a well documented radiologic and pathologic analysis is mandatory. There is only one microphotograph in this publication and it is from the rhabdomyosarcomatous component, with a small inset to depict the cross-striations. The published radiographs and photographs of the sectioned gross specimen suggest to us the presence of dense, firm matrix formation in areas. Radiographs of the amputated specimen, after soft tissue removal from the thigh, would have been very helpful. There is no follow-up, as the patient "left the hospital and never returned", after a coxofemoral disarticulation and "one course of adjuvant chemotherapy". However, it is stated that "the postoperative course was uneventful, but a nodular lesion appeared on the follow-up chest X-ray".<sup>58</sup> We presume it represented pulmonary metastases.

Rhabdomyosarcomas are very frequent tumors of the soft tissues in children.<sup>59</sup> Their distribution is characterized by a peak during the first years of life, mainly represented by tumors of the head, orbit, neck and genitourinary tract; and a second peak during adolescence where paratesticular tumors predominate.<sup>60</sup> Metastases to bone are frequent, occasionally producing multiple osteolytic lesions in numerous bones. Only very rarely do deep seated rhabdomyosarcomas extend to adjacent bones to

the extent that one must differentiate them from primary tumors of bone. Usually they limit their invasive activity to the production of cortical erosions.

There are several reports of rhabdomyosarcoma in the temporal bone of very young children. These usually represent a primary alveolar or embryonal rhabdomyosarcoma arising in the middle ear and presenting itself as a pseudo-suppurative process. The tumor, as a rule, extends to the external auditory canal as a bleeding, friable polypoid lesion and to the mastoid and internal auditory canal. These tumors produce extensive destruction of the temporal bone, intracranial invasion at the posterior fossa and multiple cranial nerve defects, especially of the seventh nerve.<sup>61</sup>

The authors are convinced that the cases reported as primary rhabdomyosarcoma of bone by Rasquel et al<sup>56</sup> and by Hsueh et al<sup>58</sup> are definitely not pure primary rhabdomyosarcomas of bone and represent a primary tumor of mixed origin composed of osteogenic and rhabdomyosarcomatous elements; in other words, primary osteo-rhabdomyosarcomas of bone.

#### Rhabdomyosarcomatous Elements in Other Primary Tumors of Bone

Rhabdomyosarcomatous elements have been reported as part of other primary tumors of bone. All these reports respond to the original event described by Dahlin and Beabout in 1971<sup>62</sup> as "*dedifferentiation*" of low grade chondrosarcomas. They studied 370 cases of well differentiated chondrosarcomas in which thirty three (10%) developed sarcomas with the histologic features and highly malignant behavior of fibrosarcoma and osteogenic sarcoma. They assumed that well differentiated cells could revert to primitive poorly differentiated ones by a mechanism which they called "*dedifferentiation*". It is not our intention at this time to elaborate on the different views pertaining to this controversy. Suffice to say that, although we favor the concept that postulates the presence of multipotential clones to explain the development of highly malignant additional mesenchymal components in low grade chondrosarcomas, there is no available data to definitely rule out the possibility of "*dedifferentiation*".<sup>63</sup> To avoid said controversy the group from the M.D. Anderson Hospital<sup>64</sup> coined the term "*chondrosarcoma with additional mesenchymal component*". However, we believe that the term "*dedifferentiated chondrosarcoma*" has been extremely useful to delineate a distinct nosologic entity with specific clinicopathologic characteristics: presence of a previous low grade chondrosarcoma which gives origin to anaplastic clones of heterologous elements, occurs more frequently in elderly patients (above the age of sixty), has an aggressive ominous prognosis and characteristic histologic and radiologic pictures. It is important to mention that the "*dedifferentiated*" highly malignant tissues are juxtaposed and sharply demarcated from the low grade chondrosarcomatous component, contrariwise to the anaplastic components of poorly differentiated chondrosarcomas in which transitions from one cell to the other could be suspected and both types of cells, highly anaplastic and less undifferentiated, intermingled among themselves.<sup>65, 66, 67</sup>

In 1978 Dahlin<sup>68</sup> enlarged his series at Mayo Clinic to

51 dedifferentiated chondrosarcomas out of 419 chondrosarcomas for a 10% transformation. The last report from the Mayo Clinic is that of Frassica et al<sup>69</sup> in 1986 where they identified 78 cases of dedifferentiated chondrosarcoma among 713 patients with chondrosarcoma treated at their institution from 1915 to 1983 for approximately an eleven percent rate. The histology of the highly malignant component in their series was as follows: 42 cases (54%) with osteogenic sarcoma (fibroblastic in thirty-two, osteoblastic in six and chondroblastic in four); 33 cases (41%) with fibrosarcoma and three patients (4%) with malignant fibrous histiocytoma.

In 1974 Mirra and Marcove<sup>70</sup> reported five additional cases of fibrosarcomatous dedifferentiation in chondrosarcoma.

In 1979 Campanacci et al<sup>71</sup> reported on twenty-five patients with dedifferentiated chondrosarcoma: 15 cases to fibrosarcoma, 5 to angiosarcoma, 3 to osteosarcoma and 2 to malignant fibrous histiocytoma.

McFarland et al in 1977<sup>72</sup> described four chondrosarcomas that initially appeared to be low grade but in which anaplastic mesenchymal components developed later. One of these four disclosed large eosinophilic cells that reportedly exhibited cross-striations characteristic of rhabdomyoblasts in light microscopy, but there was no ultrastructural nor immunopathologic confirmation. In our perusal of the literature this case most probably represents the first instance of reported rhabdomyomatous elements in dedifferentiated chondrosarcomas.

Sanerkin and Woods<sup>73</sup> (1979) reported six malignant fibrous tumors (fibrosarcomas and malignant fibrous histiocytomas) arising in cartilagenous tumors. They postulated that the malignant mesenchymal elements may arise as malignant transformation of fibrous reparative tissue surrounding the cartilagenous tumor. This theory has not gained any support as most pathologists believe that the so-called dedifferentiated focus "*arises within cartilage and represents an intralesional transformation*".<sup>74</sup> They<sup>73</sup> also considered the cartilagenous tumors as enchondromata. It is a very well recognized fact how difficult it is to determine whether an extremely well-differentiated cartilagenous lesion is benign or malignant.

McCarthy and Dorfman (1982)<sup>74</sup> reported on eighteen cases of chondrosarcoma with focal dedifferentiation. Fourteen cases showed the pattern of malignant fibrous histiocytoma, three of osteosarcoma and one case of fibrosarcoma.

Astorino and Tesluk<sup>75</sup> presented in 1985 the first documented (ultrastructurally and immunochemically) case of a chondrosarcoma with an additional rhabdomyosarcomatous component. Electron microscopy examination showed sarcomeres with actin and myosin filaments as well as "Z" bands. On immunoperoxidase staining many of the tumor cells showed a positive reaction for myoglobin.

The group from the M.D. Anderson Hospital and Tumor Institute presented 26 cases with a clinicopathologic analysis<sup>64</sup> and with an immunohistochemical and electron microscopy study.<sup>63</sup> The additional mesenchymal component was histologically classified as malignant fibrous histiocytoma in 16 cases, rhabdomyo-



sarcoma in 4, low grade fibrosarcoma in 3, osteosarcoma in 2 and undifferentiated sarcoma in 1 case.

The areas of pleomorphic rhabdomyosarcoma showed a proliferation of large, round and multinucleated strap cells. Cross-striations, visible on hematoxylin and eosin stained sections and PTAH, were further demonstrated on electron microscopic study. Immunohistochemical staining using antidesmin and antimyoglobin sera was performed on these four tumors, cells were positive for both antisera on all cases, supporting their rhabdomyosarcomatous nature.<sup>64</sup>

Niezabitowski et al (1987)<sup>65</sup> reported a case of rhabdomyosarcomatous component in a dedifferentiated chondrosarcoma. It was a lesion of the proximal left femur in a 57-year old man. Cross-striations were seen in some cells with light microscopy and also these cells were strongly positive for desmin.

Capanna et al (1988)<sup>76</sup> reviewed the cases of forty-six patients with dedifferentiated chondrosarcoma from the Rizzoli Orthopedic Institute in Bologna, Italy. The additional malignant mesenchymal component in these cases was distributed as follows: osteogenic sarcoma in 18 cases, malignant fibrous histiocytoma in 14, fibrosarcoma in 11, angiosarcoma in 2 and highly undifferentiated sarcoma in 1 cases. In this review<sup>76</sup> of the Rizzoli Institute it is stated that the forty-six patients with dedifferentiated chondrosarcoma were treated between 1937 and 1984. In view of this statement one must assume that these 46 cases represent an updating of the twenty-five cases reported by Campanacci in 1979.<sup>71</sup> We are including both series separately in Table IV with a pertinent remark. Along the same vein, the seven cases of dedifferentiated peripheral chondrosarcomas reported by Bertoni et al<sup>77</sup> in 1989 from the Rizzoli Institute are

also included separately in Table IV. It is stated in this communication<sup>77</sup> that the total number of cases of dedifferentiated chondrosarcomas in their files was 51 which represents 6 more than the total reported of 46 in a previous review.<sup>76</sup> The seven cases of peripheral dedifferentiated chondrosarcoma (arising in osteochondromas) exhibited malignant fibrous histiocytoma as the additional malignant mesenchymal component.

Scheele et al in 1990<sup>43</sup> reported, as a primary malignant mesenchymoma of bone, a tumor in the right acetabular region of a 60-year old white man. It was composed of chondrosarcomatous, osteosarcomatous and rhabdomyosarcomatous elements. Although it was reported as a primary malignant mesenchymoma of bone, the authors<sup>43</sup> described the similarities between the latter and dedifferentiated chondrosarcoma with additional mesenchymal components. They<sup>43</sup> state that if a primary malignant mesenchymoma of bone contains a chondrosarcomatous component, distinction between primary malignant mesenchymoma of bone and dedifferentiated chondrosarcoma with additional mesenchymal component "becomes difficult and somewhat abstract".

It is our contention that dedifferentiated chondrosarcoma with additional mesenchymal component is a well defined nosologic, clinical and pathologic entity which should be kept as such. The fact that there are poorly differentiated chondrosarcomatous elements does not necessarily rule out, as Scheele et al<sup>43</sup> pretend, dedifferentiated chondrosarcoma, as long as there are also adjacent elements of low grade or borderline chondrosarcoma.

Furthermore, as it is evident in our present review of the literature, the so-called primary malignant mesenchymomas of bone are basically tumors of mixed origin: nine of them composed of liposarcomatous and osteosarcoma-

Table IV

**Additional Mesenchymal Component in 217 Dedifferentiated Chondrosarcomas  
Review of the Literature**

Authors	N	Osteogenic sarcoma	Fibrosarcoma	Malignant fibrous histiocytoma	Angiosarcoma	Rhabdomyosarcoma	Undifferentiated sarcoma
Frassica et al (1986)							
(Mayo Clinic series)	78	42	33	3	-	-	-
Mirra et al (1974)	5	-	5	-	-	-	-
McFarland et al (1977)	4	1	2	-	-	1	-
*Campanacci et al (1979)							
(Rizzoli Institute)	25	3	15	2	5	-	-
Sanerkin et al (1979)	6	-	4	2	-	-	-
McCarthy et al (1982)	18	3	1	14	-	-	-
Astorino et al (1985)	1	-	-	-	-	1	-
Tetu et al (1986)							
Johnson et al (1986)							
(M.D. Anderson series)	1	-	-	-	-	1	-
*Capanna et al (1988)							
(Rizzoli Institute)	46	18	11	14	2	-	1
*Bertoni et al (1989)							
(Rizzoli Institute)	7	-	-	7	-	-	-
Total	217	69	74	58	7	7	2

\*Probably many of these cases are repeated in what appears to be mostly an updated series.

Table V

Primary Osteo-Rhabdomyosarcoma of Bone					
Author	Age	Sex	Site	Metastases	Survival
Pasquel et al (1976)	13	F	Right femur	Left-lung-eight months after dis-articulation	N.R.
*Hatlinghus et al (1986)	43	F	Upper sternum	Lung, pleura, heart, kidney	7 months after
Hsueh et al (1986)	11	M	Right femur	Lung	Lost to follow-up
Marcial-Seoane et al (1990)	12	F	Left femur	Lungs - seven months after dis-articulation	8 months after disarticulation

\*This case developed in sternum following irradiation for cancer of breast. It was reported in the literature as "malignant mesenchymoma".

Note: Pasquel and Hsueh cases were reported as primary rhabdomyosarcomas of bone. The authors consider them as osteo-rhabdomyosarcomas of bone.

tous elements and the remaining four of rhabdomyosarcomatous and osteosarcomatous components. We prefer to classify these tumors as osteo-liposarcomas and osteo-rhabdomyosarcomas.

We are not denying the possible existence of a primary malignant mesenchymoma of bone with more than two neoplastic mesenchymal tissue components. However, dedifferentiated chondrosarcoma with additional mesenchymal components should be ruled out first when chondrosarcomatous elements are present. The latter statement also applies to the other case, in which rhabdomyosarcoma, osteosarcoma and chondrosarcoma were present, quoted by Scheele et al<sup>43</sup> as reported by Sathaphatayavongs et al in the Journal of the Medical Association of Thailand (1980). There was no follow-up in this case.

It is important to signify that from a total of 217 cases of dedifferentiated chondrosarcomas analyzed from the literature only 7 cases presented rhabdomyosarcomatous components (Table IV).

If the two cases reported as primary malignant mesenchymomas of bone in Scheele's article<sup>43</sup> are added as dedifferentiated chondrosarcomas with additional mesenchymal components, the total of the latter will increase to 219 cases, with rhabdomyosarcomatous elements in 9 and osteosarcomatous ones in 71 cases.

There seems to be a consensus favoring the theory of histogenesis of multiple clones of cells with the capability to differentiate into separate lines with differing histology and level of maturation.<sup>63, 67, 78</sup>

It is of interest to speculate whether an induction process by the existing chondrosarcoma mediates in the development of the rhabdomyosarcomatous component as has been suggested to explain the rhabdomyosarcomatous component of the Triton tumor.<sup>79</sup>

### Primary Osteo-Rhabdomyosarcoma

Our review of the literature yielded only three instances of what we would consider to be primary osteo-rhabdomyosarcoma of bone.

The case reported by Pasquel et al<sup>56</sup> as a primary rhabdomyosarcoma of bone has been previously analyzed in this article. There is no doubt in our minds that it represents radiologically and histopathologically the first reported case of primary osteo-rhabdomyosarcoma of bone and not a pure primary rhabdomyosarcoma.

The second case is the one reported by Hsueh et al,<sup>58</sup> also as a primary rhabdomyosarcoma of bone; however, the radiographs disclose areas highly suggestive of osteogenic matrix formation. There is only one microphotograph and it is taken from the rhabdomyosarcomatous areas. We are certain that if the surgical specimen of the amputated extremity is carefully and extensively surveyed, areas of osteosarcoma should become evident. It was reported<sup>58</sup> that reaction bone formation was observed but no malignant osteoid was found. Such was the original first impression on the case we are reporting until the specimen was adequately studied. There is a tendency for the pathologist to select sections for microscopic studies primarily from the soft tissue areas of the lesion.

The third case was reported in a communication considering three sarcomas which developed following irradiation for breast cancer.<sup>80</sup> The patient was a 43-year old woman who underwent a left radical mastectomy and received postoperative radiation therapy with cobalt. Eight years later she developed a tumor measuring 4 x 5 cm. in the upper part of the sternum. Radiographs showed destruction of the manubrium. Previous radiographs of this region had been normal. Histologically, the



tumor, resected as a palliative measure, disclosed elements, both of osteogenic sarcoma and of rhabdomyosarcoma. It was reported as a malignant mesenchymoma of bone.

The fourth case is the object of our present report.

### Case Report

A 12-year old girl who claims that two months following trauma to the left knee developed a tender and hot swelling just above said knee. There were no lymph nodes palpable in the inguinal region.

Radiographs showed a destructive metaphyseal lesion which abutts in the epiphyseal plate of the distal left femur. Prominent cortical destruction is evident with extension of the medullary tumor to the paraosteal tissues on both lateral aspects of the lower femur. There is periosteal reaction with early Codman's triangle formation. The radiologic picture is biphasic with prominent osteolytic destruction, but also with some dense osteoblastic areas, especially evident in the lateral aspect of the lesion and in the lateral paraosteal soft tissues. (Fig. 7)



Figure 7-A. Antero-posterior view of the left knee disclosing destructive biphasic lesion in distal metaphysis with prominent lateral cortical destruction and Codman's Triangle. The growth plate is in close contact with the tumor.



Figure 7-B. Lateral view with biphasic (osteolytic and osteoblastic) metaphyseal tumor. The periosteum is elevated secondary to tumor extension to subperiosteal tissues.

All clinical tests and evaluations failed to disclose metastatic disease. A disarticulation of the left hip was performed. There was a soft tissue swelling around the distal metaphysis, most prominent over the medial and posterior aspects. (Fig. 8) The medullary cavity was expanded by an intramedullary tumor, hemorrhagic with grayish white gritty areas, which destroyed the cortex, elevated the periosteum and invaded it. (Fig. 9) The growth plate and the epiphysis were also invaded by the tumor. A popliteal lymph node was recovered from the specimen for microscopic examination.

Histologically, the tumor, throughout most of the hemorrhagic soft tissue component, was characteristic of a rhabdomyosarcoma of embryonal type. Most of the cells contained abundant eosinophilic cytoplasm and assumed racket or tadpole shape (Fig. 10). Others were elongated and of strap type. Easily identifiable cross-striations were evident in H & E sections (Fig. 11). These were definitely confirmed by electron microscopy (Fig. 12). At the time this specimen was studied (1972) immuno-histochemistry was not available.

Sections from the grayish-white gritty areas disclosed classical malignant osteoid, characteristic of osteogenic sarcoma, and other areas of fibrosarcomatous osteosarcoma (Fig. 13). Sections from the popliteal lymph node



Figure 8-A. Amputated specimen after removing adjacent soft tissues. The tumor elevates periosteum and extends to parosteal tissues medially and posterior. (Posterior view of amputated left femur).



Figure 8-B. Radiograph of the amputated femur seen in A. Notice the parosteal extension of the tumor and the well-depicted Codman's triangle. The osteoblastic matrix is very well seen.

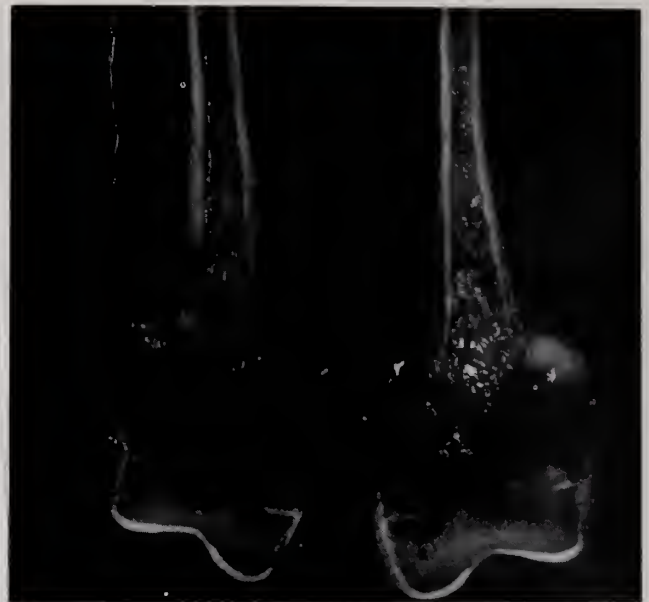


Figure 9-A. View of the halves of the bisected specimen. Medullary cavity is replaced by hemorrhagic tumor which abutts on the growth plate and also invades the epiphysis. Codman's triangles are clearly evident.



Figure 9-B. Radiographs of the bisected specimen shown in A. Notice the areas of osteogenic sarcoma with mineralized matrix.

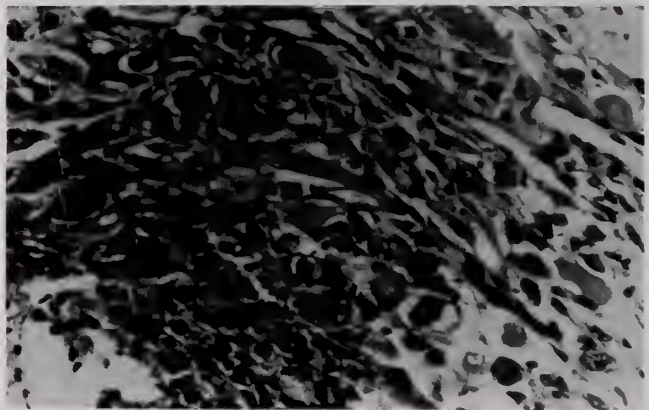


Figure 10-A. Embryonal rhabdomyosarcomatous areas disclosing varying degrees of differentiation including elongated and rounded rhabdomyoblasts. The prominent eosinophilic cytoplasm with vacuolization is partially caused by deposits of intracellular glycogen.



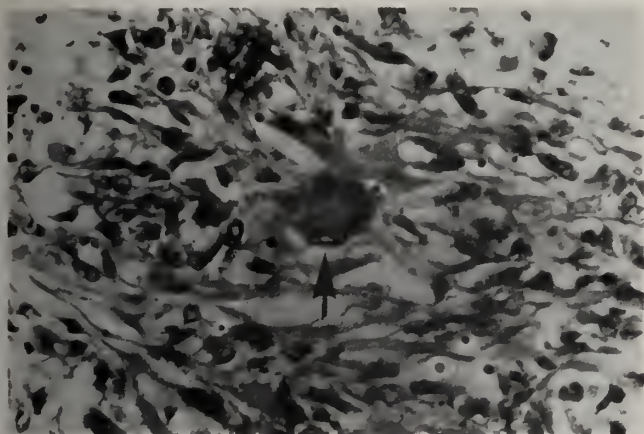


Figure 10-B. A classical multinucleated giant cell with peripherally placed "wreathlike" nuclei, a characteristic and diagnostically useful feature of rhabdomyosarcomas, mostly of the alveolar type (arrow).



Figure 12. Electron microscopy disclosing the diagnostic "Z" bands of rhabdomyoblasts (arrow).



Figure 11-A. Areas of rhabdomyosarcoma with elongated and strapped tumor cells.

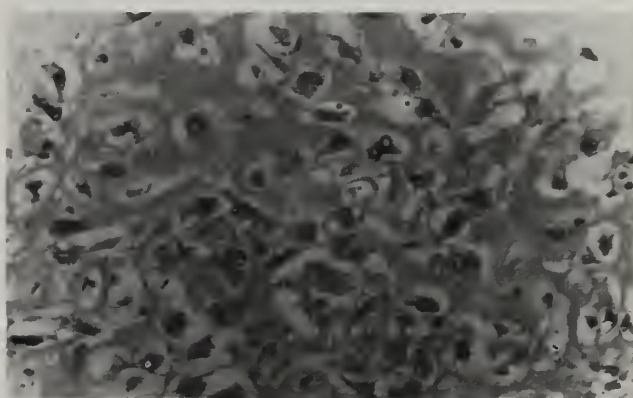


Figure 13-A. Areas of malignant osteoid matrix formation in the osteo-rhabdomyosarcoma.

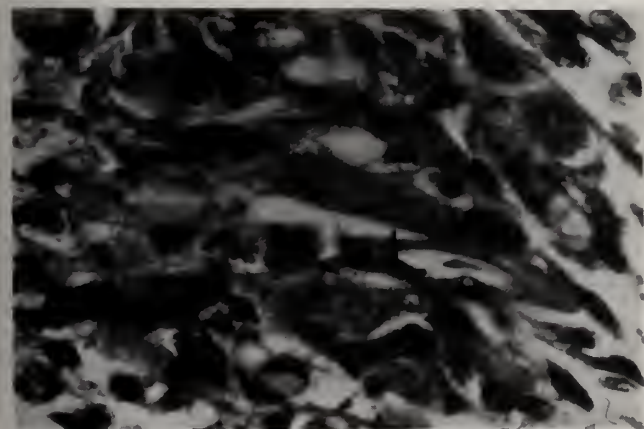


Figure 11-B. Cross-striations are evident in the large strapped cell (arrow-head) in this H&E section.

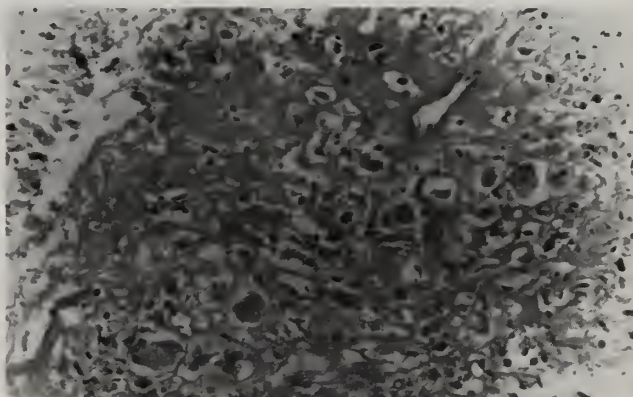


Figure 13-B. Higher magnification clearly depicting the osteogenic sarcomatous areas.

recovered disclosed embryonal rhabdomyosarcoma in one of the peripheral sinuses without extension to the rest of the lymph node. (Fig. 14)

The patient was lost to follow-up two months after surgery. She was brought by her parents seven months after the disarticulation because of stabbing chest pain during inspiration. Radiographs showed extensive pulmonary metastases extending to the right leaf of the diaphragm and to the right side of the thoracic wall. She died at home one month later. An autopsy was not performed.



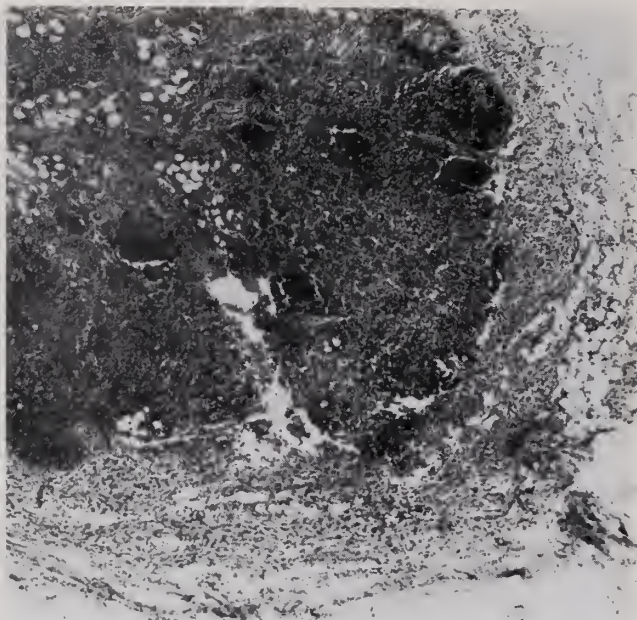


Figure 14-A. Popliteal lymph node exhibiting metastatic embryonal rhabdomyosarcoma in a peripheral sinus.

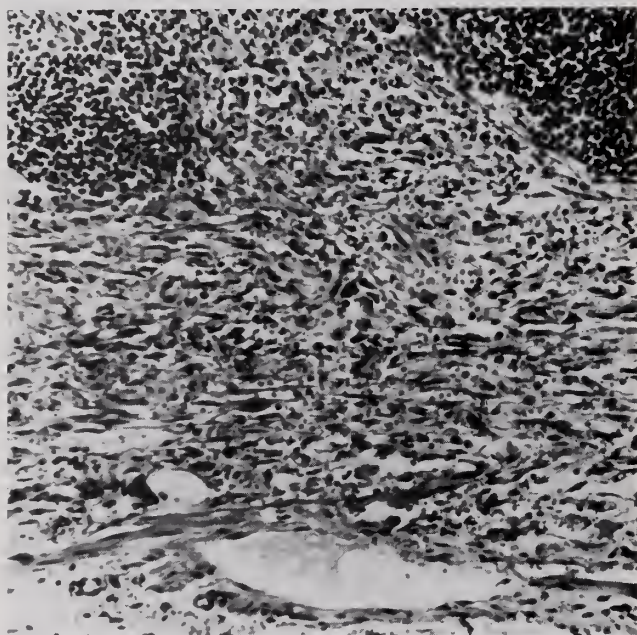


Figure 14-B. Higher magnification disclosing the classical appearance of embryonal rhabdomyosarcoma metastatic to popliteal lymph node.

**Summary:** 1. A complete perusal of the literature revealed twenty cases of primary liposarcoma of bone acceptable as such to the authors. These were tabulated as to location and age.

2. Eight cases of osteo-liposarcoma, primary in bone, were encountered in the literature and an additional case was reported by the authors.

3. The authors described for the first time in the literature a new primary tumor of bone of mixed origin: osteo-rhabdomyosarcoma. After careful perusal of the literature they added three additional cases: two cases<sup>56, 58</sup> previously reported as primary rhabdomyosarcoma of

bone, which on careful evaluation of the radiographs in said publications and the paucity of microphotographs they considered to be osteo-rhabdomyosarcomas, and the other case, previously reported as malignant mesenchymoma of the sternum following radiotherapy for breast cancer.

4. The authors prefer to classify these tumors (osteo-liposarcoma and osteo-rhabdomyosarcoma) as "Tumors of Mixed Origin" and not as "Malignant Mesenchymomas".

5. A complete review of the literature revealed 219 reported "dedifferentiated" chondrosarcomas, or chondrosarcomas "with additional mesenchymal component", among which only nine (9) contained a bonafide rhabdomyosarcomatous component. The rest exhibited other mesenchymal tumors as osteogenic sarcoma, fibrosarcoma, malignant fibrous histiocytoma, angiosarcoma, and undifferentiated sarcoma. The authors recommend to continue classifying these tumors as chondrosarcomas with additional mesenchymal component or even as "dedifferentiated" chondrosarcomas but *not* as malignant mesenchymomas.

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# Extraskkeletal Chondromas\*

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**B**enign cartilagenous tumors are relatively frequent. Their varied radiographic, histologic and clinical manifestations should always be kept in mind in their diagnostic evaluation and therapeutic considerations.

There are several important points which one must consider in the diagnosis, treatment and prognosis of these cartilagenous lesions: (1) The specific bone affected, (2) whether the lesion is centrally or peripherally located in the affected bone, and (3) if the tumor has an extraskeletal localization. In tumors with an extraskeletal location it is important to differentiate if they are associated with an articulation, intracapsular or adjacent to the articular capsule, or whether they are in the soft tissues not related to joints or bones.

The importance of the above considerations, in our experience and that of many other conversant with cartilagenous tumors, is that, in general, the clinical behavior of these tumors is more intimately correlated to location than to histologic differentiation.

We have prepared for Table I the usual classification of pure cartilagenous tumors, with some modifications, in

order to provide for the readers a source of reference whenever we mention some of them in the article. However, our main goal in this communication is not to review all the features of benign cartilagenous lesions, but to present two cases of highly unusual extraskeletal chondromas, review the literature pertaining to them, and emphasize the important correlation between clinical behavior and tumor location vis a vis histologic differentiation in benign cartilagenous tumors. Also, to present the salient radiologic and clinical characteristics of extraskeletal chondromas and their differential diagnosis.

Jaffe<sup>1</sup> since 1958 stated his empirical observation, to avoid the "overdiagnosis" of malignancy, that in evaluating histologically a cartilage lesion not contained *within* bone, a high degree of cellularity does not in itself necessarily indicate that the lesion is malignant. He found that observation useful not only in the diagnosis of juxtacortical chondroma, but also of other extra-osseous proliferating cartilage growths such as para-articular chondroma and synovial chondromatosis. This observation has been reconfirmed throughout the years and extended to the interpretation of chondromas of the soft parts.<sup>2, 3, 4, 5</sup>

It is also a well-known fact that enchondromas in the small fingers of the hands and feet practically never become malignant nor metastasize, no matter how disturbing their histologic picture may appear. Contrariwise, malignant transformation is frequent in central chondromas of the ribs and sternum and the bones of the pelvis. Enchondromas of the long bones sort of assume an intermediate position between the practically never malignant cartilagenous tumors of the small bones of the hands and feet and the frequent malignant behavior in the bones of the rib cage and pelvis. Because of the above incidence of malignant transformation, we must be thankful that enchondroma is the most frequent tumor encountered in the short tubular bones of the hands and feet, especially the former.

## Extraskkeletal Chondromas

*Intra-articular, intracapsular or para-articular chondroma* results from areas of cartilagenous extrasynovial metaplasia in the connective tissue of the outer or fibrous coat of the capsule of a joint, or in the vicinity of said capsule.<sup>1</sup> This term was coined by Jaffe,<sup>1</sup> who reported two cases within the knee joint.

These lesions may undergo a process of cartilagenous degeneration, calcification, vascularization and endochondral ossification. Because of the latter changes these chondromas have been reported as capsular osteomas,<sup>6</sup>

Table I

### Classification of Benign Chondromas

- I. Osteochondromas (Osteocartilagenous Exostoses)
  - A. Solitary
  - B. Multiple
    1. Non-familial
    2. Familial hereditary
- II. Enchondromas (Central Chondromas)
  - A. Solitary
  - B. Multiple
    1. Regional
    2. Generalized (Ollier's Disease)
    3. With hemangiomata (Maffucci's Syndrome)
- III. Juxtacortical (Periosteal) Chondromas
- IV. Extraskkeletal Chondromas
  - A. Synovial Chondromatosis
  - B. Intracapsular and Para-articular Chondromas
  - C. Soft Tissue Chondromas

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extraskelatal osteochondromas,<sup>7</sup> ossifying chondromas replacing the infrapatellar pad of fat,<sup>8</sup> ossification of intrapatellar bursae and fat pad,<sup>9</sup> and as giant intra-articular osteochondroma of the knee.<sup>10</sup>

Because, as previously mentioned, the cartilage in a para-articular or intracapsular chondroma may undergo enchondral ossification following vascular penetration of the lesion, one may encounter all the spectrum of histologic findings, from predominantly hyaline cartilage with minimal ossification to prominent ossification with residual foci of cartilage. This accounts for the variability of histologic diagnosis in these lesions.

We have attempted a perusal of the English literature on the subject in order to analyze the reported cases of intra-articular or para-articular chondromas as to location, size, age, sex, presenting complaint, and results of treatment.

Robillard<sup>9</sup> in 1941 reported what he thought to be the first case in the English literature of an intra-articular chondroma. He referred to a similar case in the French literature, reported by Redi,<sup>11</sup> with pathologic confirmation and apparently secondary to trauma. Robillard<sup>9</sup> considered the lesion as an ossification of the infrapatellar bursae and fat pad, but stated in the last sentence of the summary that "the lesion may be looked upon as an osteoma". However, there is not an adequate microscopic description of the lesion except for a photomicrograph showing bone trabeculae. He also lists in the bibliography another case of calcified pretibial bursitis by Cassou.<sup>12</sup>

Roth<sup>8</sup> in 1944 described what he and the consultant pathologist considered an ossifying chondroma producing compression atrophy of the infrapatellar pad of fat in a 69 year old man.

Kautz<sup>6</sup> in 1945 reported four cases of what he labelled as capsular osteomas of the knee joint. He also quotes in said article the studies of Kienböck in 1924,<sup>13</sup> who reported an intracapsular osteoma of the knee with a correct pre-operative diagnosis. Kienböck<sup>13</sup> was able to collect from the literature similar lesions reported by Marchand (1917), Schmidt (1918), Trapp (1896), Rumpel (1908), and by Baetjer and Waters (1921). The latter case, according to Kautz,<sup>6</sup> represented the second case of this rare lesion in the American literature. The first one was that reported by Robillard.<sup>9</sup> Kautz<sup>6</sup> with his report of four cases increased to six the reported cases in the American literature. He also mentioned eight more reported cases of osteoma of the knee joint in the world's literature: Bohm (1941), Hammer (1928) Jerusalem (1929), Laurence (1928), Razemon and Bizard (1931) Schnaberth (1937), Simon (1925), and Weiss and Lowenstein (1929).

All four cases reported by Kautz<sup>6</sup> were localized in the left knee and the lesion was demonstrable in radiographs as a well delineated shadow with bony density. There was practically no secondary change in the adjacent bone surfaces, and the tumor was not connected with bone nor with synovial tissue. In all cases the tumor was localized in a part of the anterior compartment of the knee joint beneath the patella. All the tumors were well delimited and surrounded by fibrous tissue. On section they were primarily composed of vascularized cancellous bone with

areas of hyaline cartilage. The symptoms were minimal and the limitation of joint motion was totally corrected after surgical removal of the tumor, Kautz<sup>6</sup> called these lesions *capsular osteomas* because of the preponderance of vascularized cancellous bone over its cartilagenous component. We believe these lesions present intracapsular chondromas which have undergone vascularization and enchondral ossification.

Purser<sup>7</sup> in 1956 reported two cases which he considered as *extraskelatal osteochondromata*. These two cases represented the first to be described in the foot. Suermondt<sup>15</sup> reported a primarily osseous lesion in the anterior capsule of the elbow.

Mosher and associates<sup>14</sup> reported three additional cases in 1966 and for the first time the term of intracapsular or para-articular chondroma coined by Jaffe<sup>1</sup> in 1958 is utilized in the literature. The three cases were localized in the knee joint. Two of them were primarily composed of cartilage with small areas of calcification and ossification. The third one was primarily osseous with peripheral cartilage.

Sarmiento and Elkins<sup>10</sup> (1975) reported a giant intra-articular osteochondroma of the knee. Milgram and Dunn<sup>16</sup> reported three cases in 1980, all of them in the left knee joint. An additional case, also in the left knee, was reported by Milgram and Jasty<sup>17</sup> in 1983.

Our perusal of the literature has revealed thirty-four reported cases of intra-articular or para-articular chondroma. All of them were located in the knee joint except two in the foot,<sup>7</sup> related to the metatarsophalangeal joint and one in the elbow joint.<sup>15</sup> The case subject of this report represents the thirty-fifth instance of this lesion reported in the literature. It also represents the first case reported in Puerto Rico, and, interestingly enough, the first report in the literature in which computerized tomography (CT) was utilized to ascertain the exact location and relation to bone of the lesion.

### Clinical and Radiologic Findings

These rare lesions, primarily of the knee joint, are the result of cartilagenous metaplasia in the outer or fibrous coat of the capsule or in the adjacent connective tissue of the joint. The origin is extrasynovial and should not be confused with the more frequent synovial chondromatosis in which the cartilagenous metaplasia occurs in the sublining connective tissue of the synovial membrane.<sup>1</sup>

The patients with intra-articular or para-articular chondromas usually present a history of several months, some even several years, of slight to moderate discomfort, aching, and only infrequently minimal limitation of the range of motion of the affected knee. A few may refer to a history of antedating trauma to the knee, but more often than not there is no history of trauma. Practically all patients complain of swelling because of the presence of a mass, but without evidence of inflammatory reaction and devoid of systemic signs and symptoms. More frequently than not the mass has been present for several months or even years.

Jaffe<sup>1</sup> in 1958 stated, in the report of two cases, that "the subject is likely to be a young adult". However, after our review of the literature, among those cases where the age was disclosed, 12.5% were in the third decade, 12.5%

in the fourth, 12.5% in the fifth, 25% in the sixth, and 37.5% in the seventh decade. In other words, 62.5% of the patients were older than fifty years, and 37.5% were younger than fifty, of which 25% were between twenty-three, the younger patient, and thirty-nine years of age.

No reference was found in the literature pertaining to any specific sexual preponderance in the incidence of this lesion. After analyzing the cases reported where the sex was stated, 58.8% were males, however, there were several cases in which the sex was not available. One must conclude that there is no sound evidence to ascribe any sex predilection to this lesion.

A very interesting finding surfaces in our review, one for which we do not have any reasonable explanation available: 80% of the intra-articular and para-articular chondromas of the knee joint were present in the left knee.

Radiographs usually present a well delimited mass, completely separated from bone, with irregular spotty areas of calcification or as a large, lobulated, homogeneously dense mass. The radiologic appearance obviously depends on the histologic appearance and the proportion between the amount of hyaline cartilage and the degree of endochondral ossification present in the tumor. Only rarely do there are secondary changes on the surfaces of adjacent bones as this lesion is extraosseous and not connected to periosteum or synovial surface. Mosher<sup>14</sup> in one of his cases (Case 3) suggested in the radiograph that "there appears to be erosion of the tibial plateau". Kautz,<sup>6</sup> in another case (Case 1), noticed in the X-ray that "the outlines of the tibial surface were irregular and hazy, and there was slight subchondral demineralization". Our case disclosed very well defined cortical changes in the adjacent bone, saucer-shaped with reactive sclerosis, which will be amply described later.

### Pathologic Findings

These unusual lesions present themselves as a single mass surrounded by thick collagenous fibrous tissue. They may be loose within the articular cavity or slightly attached by minimal amounts of fibrous tissue, to the surrounding outer fibrous coat of the capsule of the joint or to the connective tissue in the region of the capsule. On cut section they are composed of several lobules of cartilage separated by loose connective tissue and of areas of trabecular bone, in different proportions.

Histologically the lobules are hyaline cartilage, and the areas of ossification secondary to endochondral bone formation are evident in the vascularized areas. Areas of calcification of cartilage are also seen. The proportions of the above described tissues within the tumor will determine the gross and microscopic appearance, as well as the radiologic picture. The variability in the proportional amount of each one of these tissues is also responsible for the numerous different names given to this lesion. They have been called *capsular osteoma*,<sup>6</sup> *extraskelatal osteochondroma*,<sup>7</sup> and *ossifying chondroma*.<sup>8</sup>

The location in relation to the joint, whether intra-capsular or extracapsular, the latter not infrequently within the infrapatellar fat pad, also accounts for other names given to the lesion. Among these are *ossification of infrapatellar bursa and fat pad*,<sup>9</sup> *ossifying chondroma*

*replacing the infrapatellar pad of fat*,<sup>8</sup> and the one which we consider the most appropriate name for this lesion, intra-articular or para-articular chondroma.<sup>1</sup>

The size of this lesion almost always accounts for a palpable mass as the most important presenting complaint in the patients. Upon reviewing the literature, among those cases where accurate measurements are reported, it is evident that the lesion is discoid, if you wish patellar-shaped, with the smallest lesion measuring 4 x 4 x 2 cm. and the largest 8 x 5 x 4 cm. The immense majority of the lesions exhibit a main diameter between 5 and 6 cm.

It is our contention, as well as that of other authors,<sup>1, 14</sup> that the lesion is primarily a cartilagenous one, probably arising from metaplasia of the connective tissue of the outer fibrous coat of the joint capsule and/or the connective tissue in the vicinity of the capsule.<sup>1</sup> The lesional cartilage, arranged in lobular fashion, may show areas of degeneration and calcification and others of vascularization and enchondral bone formation. The balance between the cartilagenous and the osseous component will be the determinant factor in the macroscopic appearance of the lesion and in the radiologic picture.

It is extremely important to recognize that this lesion, as well as the soft tissue chondromas, which we will discuss later, and the juxtacortical chondroma, may disclose prominent cellularity of the cartilagenous component, with immature appearance of the tumor cells closely mimicking chondrosarcoma. One always must be conscious of the fact that said high cellularity, in extraskelatal chondromas, does not in itself necessarily indicate that the lesion is no longer benign. It is important to remember this observation in order to avoid overdiagnosing such extraskelatal benign cartilagenous lesions as malignant.

### Differential Diagnosis

A variety of osteocartilagenous lesions are found near joints. Most common among them are *osteophytes* which form at the periphery of joints with degenerative arthritis. Such lesions may occasionally be quite large, may lack direct osseous continuity with the joint surface near which they arise but may still be embedded in the articular soft tissues.<sup>16, 17</sup>

The term *osteoma* should be totally discarded as true osteomas are almost practically limited to the skull, paranasal sinuses, and mandible. The diagnosis of osteoma should not be applied to excrescences or protuberances of fibrous or cartilagenous origin that have become ossified.

The frequent *osteochondroma* that represents a continuous growth of cortex and spongiosa as a cartilage-capped protuberance is a lesion of bone which frequently occurs in the distal metaphysis of the femur and proximal one of the tibia. As they grow in the direction of the line of the pull of tendons, which is toward the diaphysis and away from the nearest epiphysis, they very rarely protrude into the joint cavity and thus become intra-articular.

Para-articular and intra-articular chondroma must be differentiated from *synovial chondromatosis* or *osteosarcoma*.



*chondromatosis*. The latter condition is usually seen in young and middle aged adults, has a predilection for the knee joint, and is practically always monoarticular.<sup>19</sup> The most important differential point is that the intra-articular bodies ("joint mice") in synovial chondromatosis are multiple, of differential sizes, and rarely larger than 1 cm. in diameter.

One must also remember that osteocartilagenous bodies in the joint may also be observed in other conditions, albeit extremely uncommon. Trauma may tear away a cartilagenous fragment from the joint surface. In *osteochondritis dissecans* a subchondral fragment of bone may be detached from the articulating surface.<sup>20</sup>

The most worrisome problem encountered in the diagnosis of these lesions is to differentiate them from *chondrosarcoma* and rarely from *parosteal osteosarcoma* and *periosteal* or *juxtacortical chondroma*. The intracapsular and infrapatellar location coupled with the absence of bone involvement militates against a primary chondrosarcoma of bone. The fact that periosteal chondroma and parosteal osteosarcoma developed from below the periosteum and are in close contact with the cortex of bone is the principal differential point. It is also pertinent to recall that periosteal or juxtacortical chondroma produces a saucer-shaped destruction of the cortex with prominent sclerosis and the presence of buttress formation in the areas where the periosteum is elevated by the subperiosteal lesion. The periosteum remains intact surrounding the periphery of the tumor. Contrariwise, the para-articular chondroma may produce a saucer-shaped indentation of the cortex of the adjacent bone with slight reactive sclerosis of the eroded cortex but there is no periosteal elevation, the lesion is completely separated from the cortical bone, thus periosteal reaction or buttress formation are not seen.

It goes without saying that para-articular chondroma only rarely may mimic radiologically paraosteal osteosarcoma in cases where the former is prominently and densely ossified. Adequate radiographic views, or CT, as in our case, establishes the separation from the cortex of para-articular chondroma. In addition, the histopathology of these two nosologic entities makes the differentiation extremely easy.

*Myositis ossificans circumscripta*, usually secondary to trauma, is another condition to be considered in the differential diagnosis. The history of trauma and the relatively short evolution of the lesion are important points in the differentiation. The radiologic diagnosis could be difficult but histologically the diagnosis is easily established.

The histopathologic features of para-articular chondromas are similar to those of other extrasynovial soft tissues chondromas. The differentiation is basically determined by the location of the former in relation to the joint.

## Case Report

A 40-year old man who has been complaining of an aching pain in the right knee for several years. No history of previous trauma was elicited. Two months prior to admission the pain became more prominent and was

accompanied by an enlargement of the medial aspect of the right knee. There was no history of acute inflammatory changes or effusions of the knee.

On physical examination he presented a mass on the medial aspect of the right knee. This mass was painless to palpation and slight motion could be elicited with pressure. There was no limitation in the range of motion of the knee. No neurovascular deficit was noted.

## Radiologic Description:

Antero-posterior radiographic view of the right knee reveals a soft tissue mass in the medial aspect, extending from the level of the medial tuberosity of the tibia to that of the medial condyle of the femur. The mass is ovoid or discoid in shape and exhibits multiple punctuate calcifications suggestive of a cartilagenous lesion (Fig. 1). An area of erosion of the cortex in the proximal tibia, adjacent to the above described lesion, is evident. There is slight reactive sclerosis at the base of the indentation but there is no periosteal reaction, evidence of buttress formation or involvement of the medullary cavity.

Computarized tomography of both knees performed at 4 mm. axial slices, with evaluation of soft tissue and bone structures, was performed. The low density lesion with multiple calcifications is noted in the medial aspect of the right knee. The lesion arises from the external surface of the medial lateral ligament and produces an indentation or cortical erosion in the medial tibial condyle. Thus the



Figure 1. Soft tissue mass with multiple punctuate calcifications medial to the knee joint.

lesion is outside the articulation or para-articular. The lesion is completely extraskeletal and there is no evidence of periosteal reaction nor of medullary cavity involvement (Fig. 2A & B).

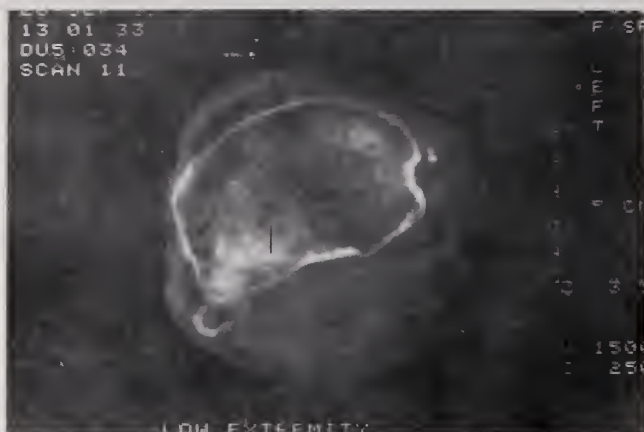


Figure 2-A. CT disclosing the cortical indented and sclerotic erosion and punctate calcifications in the adjacent pararticular chondroma.

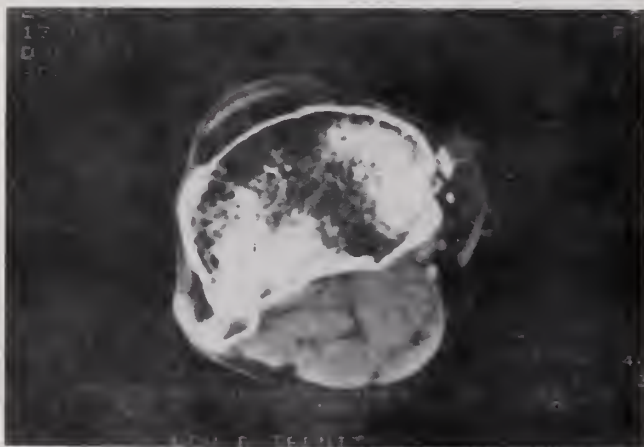


Figure 2-B. Similar to Figure 2-A but better disclosing the low density lesion with multiple calcifications.

### Operative Findings

The lesion was surgically removed without difficulty. It was found to emanate from the posterior aspect of the medial collateral ligament and was not related to bone. It was para-articular in location.

### Gross and Histologic Description:

The mass removed measures 6 x 3.5 x 1.3 cm. and is discoid or patellar shaped. The surface is covered by dense, smooth and glistening fibrous capsule. On section it is mostly composed of pearly-white cartilagenous tissue. There are some areas of calcific nature, mostly in the periphery of the lesion.

Histologically the mass is mostly composed of hyaline cartilage arranged in lobules of varying sizes and separated by fine trabeculae of vascularized fibrous tissue (Fig. 3). Calcific changes are evident in the periphery of some of the cartilagenous lobules (Fig. 4). The mass is

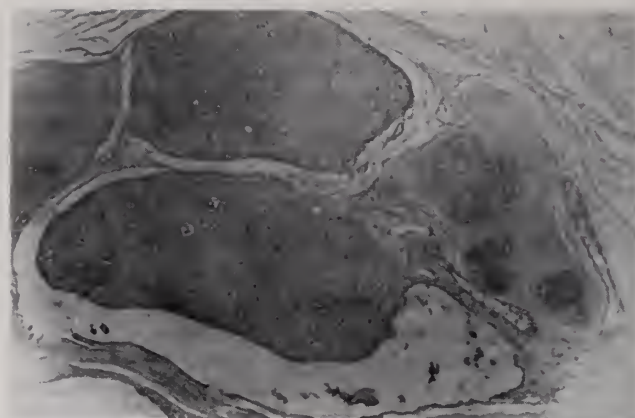


Figure 3. Lobular structure of the cartilagenous lesion with intervening vascularized fibrous septae.

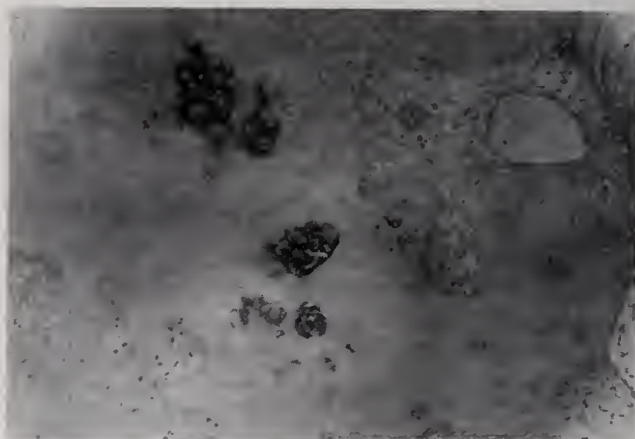


Figure 4. Calcifications at the periphery of the cartilagenous lobules of the pararticular chondroma.

surrounded by a fibrous capsule (Fig. 5). The cartilage cells are mostly well-differentiated although in areas there is increased cellularity and the presence of a few plump nuclei (Fig. 6).

*Soft tissue chondroma* is the term that we prefer to designate benign cartilagenous tumors of extrasynovial origin, primarily occurring in the soft tissues of the hands and feet, not associated with articulations, and without any connection to the adjacent bone. These lesions must be distinguished from the not infrequent cartilagenous rests of branchial origin in the lateral neck of infants and children<sup>21</sup> and from metaplastic cartilage that is encountered in various benign lipomatous and fibromatous neoplasms and from cartilage occurring within lesions of traumatic myositis ossificans.<sup>22</sup>

In 1964 Lichteinstein and Goldman<sup>2</sup> reported ten benign cartilagenous tumors in the hands and feet. Specifically, 7 were in the hand (3 in the palm, 2 in a nail bed, and 2 in a finger) and three were in the foot (2 in the ankle region and 1 in a toe). All the patients were adults whose ages ranged from 20 to 59 years. The duration of the symptoms prior to surgery varied from a few months to as long as 6 years. Four of these tumors were composed of hyaline cartilage and none of them recurred after local excision. The other six tumors were of less differentiated



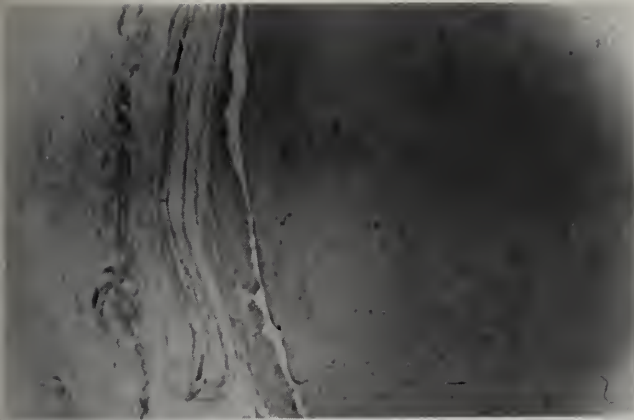


Figure 5. The pushing margins of the tumor surrounded by a fibrous capsule.



Figure 6. Cartilage cells are well-differentiated in most areas of the lesion.

chondroid nature and half of them recurred locally, requiring further surgery for effective control. In only instance did amputation eventually became necessary. No tendency whatsoever to metastasize was noted. These observations indicate that cartilage tumors of the soft tissues are not necessarily serious in spite of their frequent aggressive looking histology. From the pathologic examination alone one might have been inclined to overestimate the potential seriousness of a number of these tumors.

Dahlin and Salvador, in 1974,<sup>3</sup> reported 70 tumors of hyaline cartilage in the soft tissues of the hands and feet. Although there were recurrences in 12 of them, no lesion was associated with proved or suspected metastasis. It is of interest to note that 59 of these 70 tumors reported were referred for consultation to Dahlin because of difficulty in pathologic diagnosis. Most of them were originally considered chondrosarcomas and many of the other were considered "worrisome". It is important to emphasize that in no instance did a soft tissue cartilaginous lesion of the hand or foot gave rise to known metastasis. Most of these tumors are considered to be derived from extra-articular synovial origin.<sup>2, 3</sup> Histologically, the tumors were composed of usually lobulated hyaline cartilage, infrequently partially myxoid. In 38 cases calcifications or ossification was seen in histological

sections and it was evident in roentgenograms of 22 of 37 cases<sup>3</sup> in which reports were available.

The fact that in 9 of the 70 cases<sup>3</sup> xanthoma-like zones were present lend evidence that some of these chondroid lesions are of synovial derivation. Dahlin states that "in only a few tumors could synovial origin be deduced with certainty".<sup>3</sup> It is our contention that some of these tumors,<sup>2, 3</sup> especially those located next to joints, are para-articular chondromas as the histologic findings in both lesions are similar.

Chung and Enzinger<sup>4</sup> in 1978 reported 104 cases of chondromas of the soft parts collected over 23 years at the Armed Forces Institute of Pathology. This tumor occurred predominantly in the third and fourth decades and affects primarily the soft tissues of the hand (64%) and feet (20%). Thus 84% of these chondromas of soft tissues were localized in the hands and feet.

Almost invariably the tumors originated in the extremities, 75 in the upper and 25 in the lower extremity. Only 4 instances of the 104 cases reported were not located in the extremities, thus 96% of the lesions originated in the extremities.<sup>4</sup>

It is of interest to note that in Chung and Enzinger<sup>4</sup> series of 104 soft tissue chondromas only 15 were not localized in the hands and feet and only one case was reported in the upper arm, as is the case in our report.

Humphreys et al<sup>5</sup> in 1986 reported fifteen cases of soft tissue chondroma. Most of these lesions<sup>5</sup> occur in the extremities, seven affecting the hand and five the foot, being predominantly located on the digits. Single examples arose adjacent to the head of the fibula, in the suprascapular soft tissues and in the subcutaneous tissue of the thigh. Of the fifteen patients, eight were female and seven male. Their ages ranged from 15 to 79 years, with an average of 42.1 years. Histologically, these tumors were largely composed of adult-type hyaline cartilage, but in all cases there were foci of nuclear atypia and pleomorphism. None of the seven cases for which follow-up information was available recurred or metastasized.<sup>5</sup>

### Clinical and Radiologic Findings

The clinical manifestations of these lesions are neither striking or characteristic. The usual presenting symptom is a slowly growing mass, only rarely causing pain or tenderness. The length of the time between the discovery of the mass and its removal varied from 2 weeks to 20 years, with a median of 1.5 years.<sup>4</sup> Although nearly four fifths of the patients did not provide any information as to the presence or absence of trauma, 16 claimed that trauma or injury in the area of the tumor preceded its development.<sup>4</sup>

In all cases the extraskeletal location of the lesion was confirmed by radiographs or the operative findings or both.<sup>4</sup> Many of the radiographs showed calcifications of variable density. All the tumors were located outside the periosteum and only some exhibited cortical erosion or compression deformity with cortical sclerosis. The underlying bone and its medullary cavity were never involved and no radiologic changes suggestive of osteochondroma or enchondroma were seen. Neither were there multiple tumors nor free chondroid bodies as in synovial chondromatosis.<sup>4</sup>

## Pathologic Findings

Soft tissue chondromas are usually well demarcated or circumscribed and lobulated, chiefly composed of hyaline cartilage. Some are undergoing fibrosis or ossification at the periphery of the tumor lobules. Others are partially or completely calcified. Nearly all measured less than 3 cm. in diameter and the largest 6.5 cm. in greatest diameter.<sup>4</sup>

In about 10% of the cases<sup>4</sup> a focal, granuloma-like proliferation of epithelioid cells and giant cells of the osteoclastic type is evident. In several tumors the cartilage was less mature and approaching the appearance of chondroblasts. These cells were markedly eosinophilic and their nuclei were plump, rounded or spindle-shaped. Occasional mitotic figure was observed in some of the cells, atypical mitoses were absent.<sup>4</sup> Focal myxoid and cystic changes were prominent in some of these cases. Most of the tumors in Chung and Enzinger series were intimately associated with dense fibrous tissue suggesting tendon or aponeurosis.<sup>4</sup>

Despite the slight cellular pleomorphism and the plump appearance of many cartilage cells in the chondroblastic variants no evidence was present that these tumors behave differently from those composed predominantly of adult-type hyaline cartilage.<sup>4</sup> Multiple recurrences or metastatic lesions were not recorded after a median follow-up period of 5.7 years.<sup>4</sup> Thus, complete local excision appears to be the treatment of choice.

## Case Report

A 45-year old woman with a history of diffuse, nontoxic goiter and fibrocystic condition of the breast, who complained of a painless, slow-growing soft tissue mass in her right arm. An incisional biopsy was performed in one of the regional health centers and referred to Ramón Ruíz Arnau University Hospital. Histologically the lesion was composed of chondroid tissue with prominent cellularity and some worrisome features. Further evaluation and complete excision with adequate margins was recommended.

Clinical evaluation failed to disclose any findings except for the firm soft tissue mass in the postero-lateral aspect of the right deltoid region, movable and located at the site of a well-healed surgical incision representing the previous incisional biopsy. Radiographs failed to disclose calcifications, but a fairly well-delimited area of increased density was evident at the site of the mass. A wide excision of the mass, together with the scar of previous biopsy, was performed.

## Pathologic Description

The mass was ovoid, measuring 2.5 x 2.0 x 2.0 cm., surrounded by an adequate margin of adipose tissue and attached to the surgical scar in the skin and subcutaneous tissues from previous incisional biopsy. The mass disclosed a lobulated appearance and the cut surface was grayish-white, smooth, and slightly slimy. The borders were cell-delimited and characteristic of "pushing margins" growth. No gross calcifications were seen.

Microscopically, the dermis and subcutaneous tissues at the site of the previous excision discloses chronic

inflammatory changes with foreign reaction to suture material. No tumor cells are seen in those areas.

The periphery of the tumor is bosselated with occasional knobby projections. It is completely surrounded by dense, compressed fibrous tissue which is not infiltrated by tumor cells. The peripheral margin is characteristic of "pushing borders". (Fig. 7)

The tumor mass is mostly composed of hyaline cartilage arranged in lobules separated by fine fibrous trabeculae (Fig. 8). Most of the cartilage is mature; however, there are several areas of immature cartilage exhibiting plump nuclei with prominent hyperchromatism (Fig. 9). There are no foreign or osteoclastic giant cells which have been described in about 10% of cases of soft tissue chondromas in granuloma-like proliferation, usually in the periphery of the tumor or along the interlobular vascular channels.<sup>22</sup> In some areas the tumor is composed of immature myxomatous chondroid mesenchymal tissue resembling a myxoid chondrosarcoma. (Fig. 10) Areas of very early ischemic necrosis are evident, some with cystic degeneration.

The patient was recently seen at our University Hospital and appears to be free of recurrent or metastatic disease. The local operative site failed to disclose any clinical and radiologic evidence of recurrence. Radiographs of the chest are free of tumor.

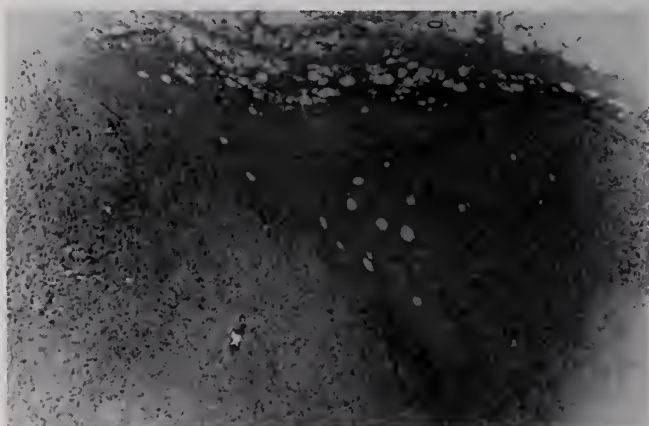


Figure 7. Nodular aspect of the soft tissue chondroma with pushing margins surrounded by dense fibrous tissue.

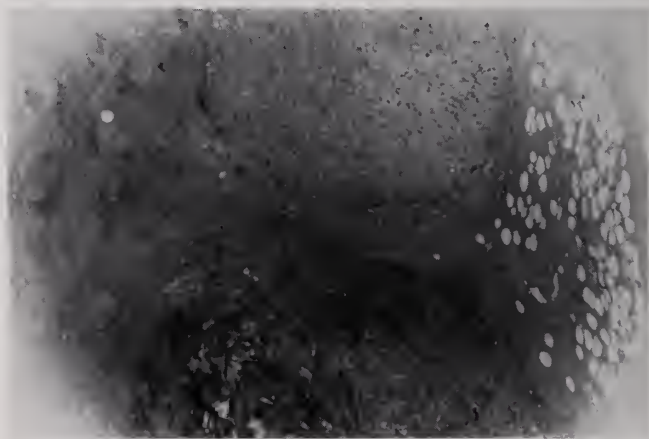


Figure 8. Lobular structure of the lesion. The lobules are composed of hyaline cartilage.



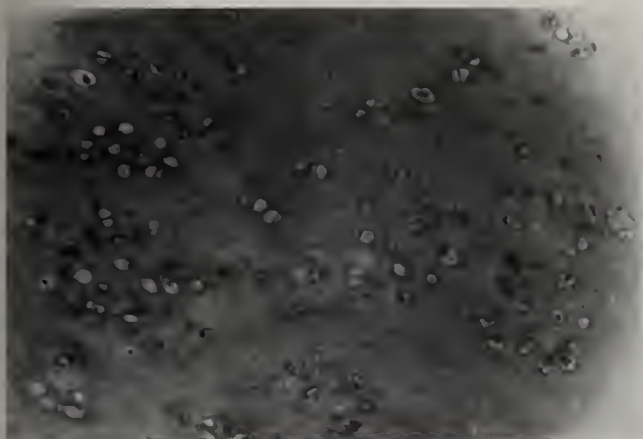


Figure 9-A. Fairly well mature hyaline cartilage in most areas of the lesion.



Figure 9-B. Immature cartilage exhibiting plump nuclei and prominent hyperchromatism.



Figure 10. Areas of immature myxomatous chondroid tissue resembling a myxoid chondrosarcoma.

**Summary:** 1. Extraskelatal chondromas occur in three variants: (a) as multiple nodules of synovial chondromatosis within a joint, (b) as a solitary lesion in association with articulations, within or adjacent to them, and (c) as an isolated cartilagenous lesion in the soft tissues, mostly of the hands and feet.

2. There are no histological characteristics which could differentiate articular, para-articular and soft tissue chondromas among themselves.

3. The latter two groups of extraskelatal chondromas are rare and frequently exhibit areas of immature cartilage with worrisome histologic features which could mislead the pathologist to an overdiagnosis of chondrosarcoma.

4. As a general rule, no matter how worrisome the histologic appearance of an extraskelatal, well delimited cartilagenous tumor may be, metastasis have not been recorded. Local recurrences are not infrequent after inadequate surgical removal; however, the tumor can always be controlled by adequate wide re-excision or resection.

5. Two cases of extraskelatal chondromas, one para-articular in the knee and the other in the soft tissue of the arm, have been presented with an exhaustive review of the literature on the subject.

6. It is of interest to note that our para-articular chondroma represents the first case reported in the literature where computerized tomography was utilized in the diagnosis.

7. The location of a soft tissue chondroma in the upper arm is extremely rare and only one previous case has been reported in said location.<sup>4</sup>

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# Basic Science Research

## Differential Antagonism by Amiloride and Pirenzepine of the Muscarinic Receptors of Rat Tracheal Smooth Muscle

Guido E. Santacana, PhD<sup>1</sup>  
Walter I. Silva, PhD<sup>2</sup>

**Abstract:** Amiloride (AM) is a well known potassium sparing diuretic. The effects of AM at the cellular level include blockade of Na<sup>+</sup>/H<sup>+</sup> exchange in several tissues and inhibition of passive sodium flux in epithelial cells. In this study we have explored the interactions of amiloride with muscarinic receptors, using isolated rat tracheal rings and compared its effects to those of the muscarinic receptor subtype-selective antagonist pirenzepine (PZ). The results obtained demonstrate the ability of AM (100  $\mu$ M to 1 mM) to inhibit the ACh induced rat tracheal contractions. The inhibition resulted in the reduction of the E<sub>max</sub> values of ACh in this preparation, and the apparent K<sub>i</sub> for AM was of 478  $\mu$ M. This effect was also observed in a sodium-free choline medium, indicating that it is independent from sodium transport mechanisms sensitive to AM. In contrast to AM, PZ displayed a surmountable type of antagonism with a pA<sub>2</sub> value of 6.52. The results demonstrate a differential antagonism by AM and PZ of the muscarinic receptors present in the smooth muscle of the rat trachea.

The therapeutic value of the diuretic amiloride (AM) in the treatment of hypertension and edema is based on its ability to produce diuresis and natriuresis while preventing significant loss of K<sup>+</sup>. This action has been postulated to be directly related to an inhibitory effect of this drug on passive sodium transport in tight epithelia of the distal tubules.<sup>1</sup> Other sodium transport mechanisms that are also inhibited by AM include the Na<sup>+</sup>/H<sup>+</sup> exchange system<sup>2</sup> and the Na<sup>+</sup>/Ca<sup>++</sup> exchange mechanism.<sup>3</sup>

In addition to its diuretic effects, AM has been shown to produce vasodilatation both "in vivo"<sup>4</sup> and "in vitro".<sup>5</sup> This effect has been ascribed to a competitive interaction of AM with the alpha adrenoceptors of vascular smooth muscle.<sup>6</sup> Relaxant effects of AM are not only observed in

vascular smooth muscle. Contraction of smooth muscle in guinea pig taenia cecum and chicken gizzard has been shown to be inhibited by AM.<sup>7</sup> A similar effect has been reported for guinea pig,<sup>8, 9</sup> and canine<sup>10</sup> tracheal smooth muscle.

Several mechanisms have been postulated to explain the inhibitory effects of AM on smooth muscle contraction. Of our particular interest is the ability of AM to inhibit cholinergic responses mediated by muscarinic receptors. Kiuipers et al (1981)<sup>11</sup> demonstrated a cholinergic antagonism of AM in rabbit pancreas. The antagonism of AM apparently results from its ability to directly bind the muscarinic ACh receptor (mAChR) present in this tissue. The importance of this muscarinic receptor blockade is two-fold. First some of the side effects of AM can be attributed to its muscarinic antagonism. Secondly, it seems that amiloride and other sodium channel blockers share the ability of interacting with muscarinic receptors. The primary goal of this study is to describe the effect of AM on the mAChR-mediated contractions of the smooth muscle of rat trachea. In addition the tracheal mAChR population was characterized using the mAChR-selective antagonist pirenzepine (PZ). A comparison of their interactions revealed a differential mechanism of antagonism. This work was previously presented in preliminary form.<sup>12</sup>

### Methods

**Rat trachea preparation.** Sprague Dawley male rats (200-300 g) were used throughout this study. The rats were anesthetized with pentobarbital (1 mg/kg) and a 9-12 mm section of the trachea was quickly excised and cleaned in cold Krebs Ringer Bicarbonate (KRB) with the following composition (millimolar): NaCl, 118; Na(HCO<sub>3</sub>), 25; KCL, 4.7; CaCl<sub>2</sub>, 3; MgSO<sub>4</sub>, 2.4; KH<sub>2</sub>PO<sub>4</sub>, 1.2; and Glucose 10.6. The excised trachea was suspended in KRB in a tissue chamber (25 ml, Rau Scientific) by using two platinum wire hangers as described elsewhere.<sup>13</sup> Cotton thread was used to secure the hangers to the tissue chamber and the force transducer (Grass FT 03 D). The KRB solution bathing the trachea was maintained at 37°C by the use of a Haake Buchler water recirculator and temperature controller. Aeration for the KRB was provided by a gas mixture of 95% O<sub>2</sub> and 5% CO<sub>2</sub>. The

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tracheal preparation was preincubated for one hour in the KRB. During this time the KRB was replaced every 15 minutes with fresh solution. The tension on the preparation was maintained at 0g during the preincubation period. A resting tension of 2g was applied afterwards and the trachea was equilibrated under this tension for an extra 30 minutes. Non-cumulative isometric contractile dose-response curves for ACh were then obtained from the rat tracheal preparation. After the control ACh dose-response curve the trachea was equilibrated for one hour with PZ (1-50  $\mu$ M) or AM (100  $\mu$ M-1 mM). At the end of this drug-equilibration period a dose-response curve for ACh was obtained in the presence of the corresponding dose of PZ or AM.

**Data analysis.** Dose response curves of ACh in the absence and presence of PZ and AM were analyzed according to the following equation using the Fit-Function procedures available in RS1 (BBN Software Products Corp., Cambridge, MA):

$$R = \frac{E_{\max} [ACh]}{[ACh] + EC_{50}}$$

where, R=response (basal tension, gms),  $E_{\max}$  = maximal response, [ACh] = concentration of ACh applied, and  $EC_{50}$  = concentration of ACh required to achieve half-maximal responses. The competitive antagonism displayed by PZ was analyzed by means of the Schild equation (14):

$$\log DR - 1 = n \log[PZ] + pA_2$$

where, DR=ratio of the doses of ACh required to obtain a 50% level of response in the absence and presence of PZ, n=the Schild slope, [PZ]=concentration of PZ (1-50  $\mu$ M), and  $pA_2$  = the concentration of PZ required to shift ACh's dose response to the right by a factor of 2. The apparent  $K_i$  of AM in its inhibition of the maximal responses of ACh was obtained using non-competitive antagonism kinetics:

$$E_{\max I} = \frac{E_{\max}}{1 + I/K_i}$$

where,  $E_{\max I}$  = maximal response observed in the presence of a given concentration of antagonist (AM),  $E_{\max}$  = maximal response of the control group, I = concentration of antagonist (AM), and  $K_i$  = apparent inhibitory constant of AM.

## Results

**Antagonism by amiloride of the muscarinic cholinergic responses of rat trachea.** The non-cumulative dose response curves for ACh yielded an  $EC_{50}$  = 14.2(±6)  $\mu$ M and an  $E_{\max}$  = 51.5 (±6.2), n=36. When the tissue was pre-equilibrated and incubated with various doses of amiloride (100  $\mu$ M-1 mM) a dose-dependent decrease in the  $E_{\max}$  values for ACh was observed (Figure 1). In order to determine if the effect of amiloride was related to the well known inhibitory action of this drug in the  $Na^+/Na^+$  exchange system of the muscle cells, the effect

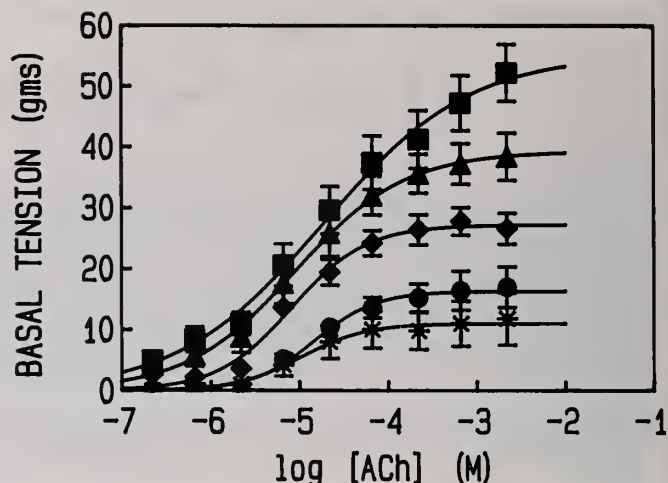


Figure 1. Dose response curves of acetylcholine in rat tracheal smooth muscle in the absence (■) and presence of 100  $\mu$ M AM (▲), 250  $\mu$ M AM (◆), 500  $\mu$ M AM (●), and 1 mM AM (\*). Each point represents the mean (± SD) from five different experimental determinations.

of 1 mM amiloride on the dose-response curve of ACh was evaluated in a sodium-free, choline-substituted KRB a condition known to depress the activity of the sodium/proton exchange mechanism. The results displayed in figure 2 show that amiloride is still able to non-competitively antagonize ACh's action in a sodium-free media. The apparent  $K_i$  value for amiloride, derived using non-competitive antagonism Kinetics, was=478  $\mu$ M.

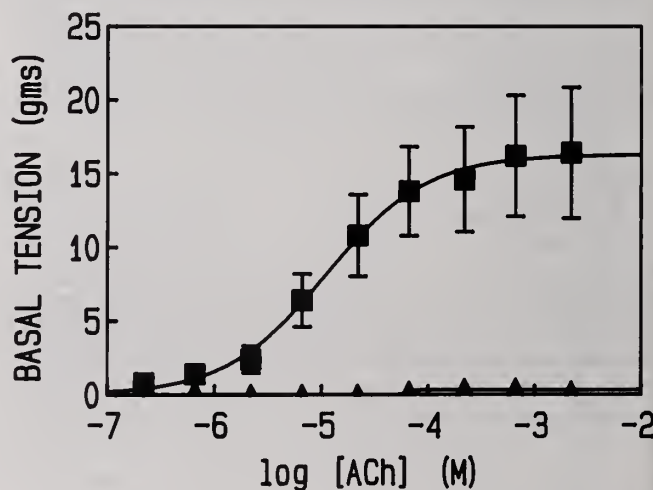


Figure 2. Dose response curves of acetylcholine in rat tracheal smooth muscle in a sodium-free, choline-substituted medium. Control (■) curves and curves obtained in the presence of 1 mM amiloride (▲). The results are the means of five different experimental determinations.

**Competitive antagonism by pirenzepine of the muscarinic cholinergic responses of rat trachea.** Studies with PZ were conducted for two main reasons. First, to our knowledge the muscarinic receptor of rat trachea has not been defined as M1 or M2 (15-17). The muscarinic receptor present in the trachea of other species (guinea pig, human, and rabbit) has been characterized pharmacolo-



gically as one with low affinity for the antagonist PZ, also known as M2 receptors. Second, and more important, was to compare the type of antagonism of PZ with the one produced by AM. This is important since typical neurotransmitter/hormone receptor antagonists are known to display a tissue-dependent antagonist behavior. This comparison will allow us to determine if the non-competitive antagonist behavior of AM is a function of the rat tracheal tissue.

As depicted in figure 3, PZ (1-50  $\mu$ M) shifted the dose-response curve of ACh to the right in a parallel manner. This behavior is typical of competitive or surmountable antagonists. Analysis of the data with the Arunlakshana-Schild equation yielded a  $pA_2$  value for PZ of 6.52. This  $pA_2$  value of PZ is characteristic of its interaction with M2 muscarinic receptors.

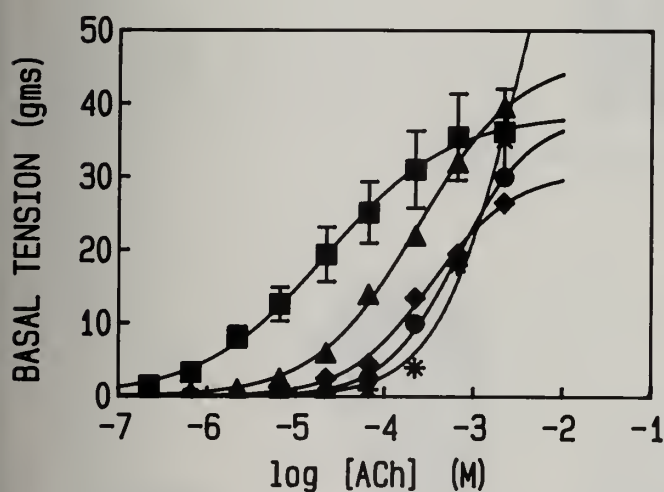


Figure 3. Dose response curves of acetylcholine in rat tracheal smooth muscle in the absence (■) and presence of 1  $\mu$ M PZ (●), 10  $\mu$ M PZ (◆), and 50  $\mu$ M PZ (\*). The values presented represent the mean of five experimental determinations.

### Discussion

The diuretic AM inhibits the ACh-induced contractions of the smooth muscle of the rat's trachea in a dose-dependent manner. The inhibition resulted in a reduction of the  $E_{max}$  values for ACh. Using non-competitive inhibition kinetics the apparent  $K_i$  for AM is of 478  $\mu$ M. In this study we also compared the antagonism of AM with the one elicited by the M2-selective muscarinic receptor antagonist PZ. In contrast to AM, PZ clearly produced a surmountable (competitive) type of antagonism. The  $pA_2$  value obtained for PZ (6.52) agrees with the values reported for M2 muscarinic receptor subtypes, and those reported for PZ in the tracheal smooth muscle of other species.<sup>16, 17</sup>

The inhibitory effect produced by AM of the ACh-induced contraction of rat tracheal smooth muscle could be related to blockade of the  $Na^+/H^+$  exchange system or to an interaction with the smooth muscle's mAChR population. The inhibitory effect by AM prevails even under conditions in which the  $Na^+/H^+$  exchange is inhibited (figure 2). This observation suggests that AM

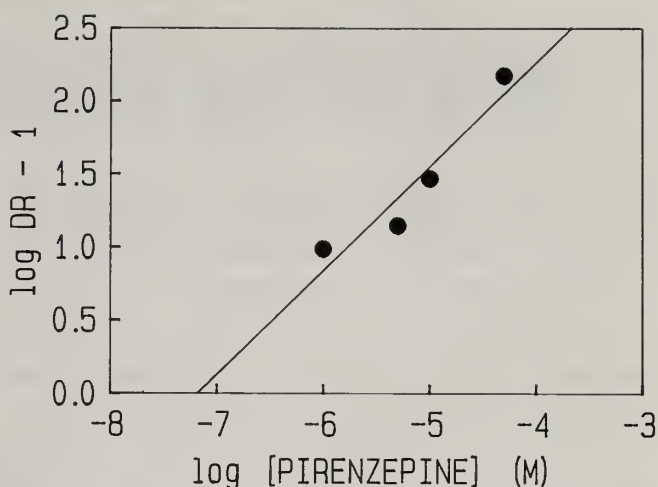


Figure 4. Schild regression plot of pirenzepine in the rat trachea. Abscissa: logarithm of molar concentrations of PZ. Ordinate: logarithm of equiactive dose ratios of ACh-I.

exerts its effects via a direct interaction or binding to the mAChR present in this isolated organ preparation. Cholinergic antagonism by AM has been previously described in rabbit pancreas, where AM competitively inhibits the specific binding of the non-selective muscarinic receptor antagonist [ $^3H$ -QNB] (quinuclidinyl benzilate) to rabbit pancreatic acini.<sup>11</sup> Similar antagonism has been observed in rat brain crude synaptosomal preparations.<sup>12</sup>

Other smooth muscles where the effects of AM have been described are, the guinea pig taenia caecum and chicken gizzard.<sup>7</sup> In these experimental preparations the authors ascribed the inhibitory actions of AM on the  $K^+$ - and Carbachol-induced contractions of these smooth muscles to the ability of AM to inhibit the myosin light chain kinase activity. Even though this effect can not be ruled out in the rat tracheal smooth muscle, the strong similarity between the apparent  $K_i$  value obtained for AM in the rat trachea (478  $\mu$ M) and its  $IC_{50}$  value of 222  $\mu$ M obtained in the binding assays of rat brain muscarinic receptor<sup>12</sup> strongly suggests that AM is exerting its effect by virtue of its capacity to interact with the mAChR receptors of the rat trachea. The fact that AM behaves competitively in rat brain and other tissues<sup>6, 11, 12</sup> suggests that AM is very likely a non-equilibrium competitive antagonist of the mAChR receptors of the rat trachea, rather than a pure non-competitive antagonist.

Interestingly, AM is capable of producing a relaxant effect on dog tracheal smooth muscle.<sup>10</sup> This relaxation elicited by AM has been ascribed to AM's inhibition of the  $Na^+/H^+$  exchange system of this preparation. The relaxation was observed in tracheal rings pre-contracted with carbachol or KCl. Using the same experimental protocol we have obtained similar results when using carbachol in rat tracheal smooth muscle (Santacana and Silva, unpublished results). Nonetheless, when rat tracheal rings are pre-contracted with ACh, and AM is added at the plateau of the contractile response, a "paradoxical" potentiation of ACh's effect is obtained (Santacana and Silva, unpublished results). Preliminary results suggest

that this potentiation is related to the ability of AM to inhibit the acetylcholinesterase activity of this tissue, a neostigmine-like action.

These observations lend further support to the fact that AM is definitely a drug with a wide spectrum of pharmacological interactions. This is indicative of the obvious difficulty in ascribing its effects on whole organ preparations to specific target molecules (receptors or enzymes). In relation to the cholinergic system of rat trachea its complexities are evidenced by its atropine-like and neostigmine-like pharmacological actions. The opposing physiological responses elicited by AM, relaxation versus potentiation of contraction, may partially explain the minimal incidence of anti-cholinergic side effects reported with AM. Still though these may be of important clinical significance in the management of edema, hypertension and primary hyperaldosteronism in patients with obstructive pulmonary conditions, and with sub-clinical asthma. Finally, administration of AM, as any other drug(s) with anti-muscarinic properties, should be seriously evaluated in the treatment of the above conditions in the elderly patient population.

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# Equilibrium Kinetics Model for the cGMP-Stimulated Phosphodiesterase of Brain Coated Vesicles

Walter I. Silva, PhD<sup>1</sup>  
Saul Puszkin, PhD<sup>2</sup>

**Abstract:** An equilibrium kinetics model is proposed to described some of the enzymatic properties of the cyclic GMP-stimulated phosphodiesterase activity associated with brain clathrin coated vesicles. The model assumes the presence of pharmacologically distinct regulatory and catalytic domains in the enzyme. The model contemplates that random fashion occupancy of the regulatory site by the substrate, cyclic GMP, induces a conformational change which leads to the generation of an activated catalytic state. Therefore, cyclic GMP is a positive allosteric modulator of the coated vesicle enzyme. Experimental data revealed that occupancy or activation of the regulatory site was not essential for catalysis to occur since hydrolysis occurred after loss ( ~ 200%) of the activation by cyclic GMP. This constitutes an example of non-essential substrate activation. Analysis of this PDE following activation by cGMP and after loss of the regulation, activation capacity of the enzyme allows the calculation of the various kinetic parameters inherent in the model.

In previous reports we described a type II phosphodiesterase (PDE) and muscarinic acetylcholine receptors in brain coated vesicles (CV), organelles that are involved in membrane recycling and receptor-mediated endocytosis.<sup>1, 2</sup> Type II PDE are phosphodiesterases whose cyclic AMP (cAMP) hydrolytic activity is stimulated by cyclic GMP (GMP). This PDE type was originally found in cytosolic fractions from liver, and has since been detected in both soluble and particulate fractions from tissues such as thymus, brain, kidney and heart.<sup>3, 4</sup> Immunological analysis using monoclonal antibodies revealed that type II enzymes constitute one of the predominant forms of PDE in the cytosol of most tissues.<sup>5</sup> Expression of type II PDE in cultured dog kidney cells can be induced by treatment with butyrate.<sup>6</sup> Conversely, its expression is diminished during transformation of 3T3-LI preadipocytes or dexamethasone treatment of cultured hepatoma cells.<sup>6</sup>

Similar to the calcium-calmodulin-stimulated PDE (type I PDE), the stimulation index of type II enzymes varies widely (0.5 to 60). The stimulation by cGMP is dependent on proteolysis, degree of purity, pH, storage and the overall stimulation index for particulate forms of the enzymes is generally lower.<sup>7-13</sup> In addition, the optimal concentration of cGMP for stimulating hydrolysis is usually higher for the particulate form of the enzyme.<sup>14</sup> The enzyme hydrolyzes both cyclic nucleotides with a  $K_m$  close to 10  $\mu$ M and 30  $\mu$ M for cGMP and cAMP, respectively. The kinetics of hydrolysis positive cAMP, respectively. The kinetics of hydrolysis suggest positive cooperativity, as revealed by Hill slope values greater than one for both cyclic nucleotides.<sup>2, 8, 9, 15</sup> Activation of cAMP hydrolysis by cGMP and other analogues shifts the dose-response curve to the left, returns the Hill slope values to unity, produces no changes in  $V_{max}$ , and enhances proteolysis of the catalytic domain.<sup>2, 4, 14, 15, 16</sup>

A two-step model was proposed for the type II PDE of rat liver<sup>16</sup> where the first step (activation process) is rather specific for cGMP, in contrast to the second step (hydrolytic process). Indeed, pharmacological studies revealed distinct activation (regulatory) and catalytic sites on the mammalian enzyme (E) and the type II PDE of the slime mold *Dictyostelium discoideum*; yet, the latter is a cGMP-specific enzyme which does not recognize cAMP at either site.<sup>16, 17</sup> In several aspects, the type II PDE activity we detected in brain CVs (2) resembles that of other tissues examined. Here we describe an alternate equilibrium kinetics model for the type II PDE of brain CV fractions which in principle applies to both particulate and cytosolic type II PDEs.

## Methods and Materials

**Coated Vesicle Preparation:** CVs from bovine brain were prepared by modifying the method of Keen *et al.*<sup>18, 19</sup> Beef brains were obtained from a local slaughterhouse, the meninges removed and the gray matter separated from the white by suction. Everything was done at 4°C in the presence of a cocktail of proteolytic inhibitors. The gray matter was resuspended in 0.1 M MES buffer, pH 6.5, 1 mM ethylene glycol-bis (B-amino ethyl ether) N,N'-tetraacetic acid, 0.5 mM  $MgCl_2$ , 0.02% sodium azide plus 0.3 mM phenylmethylsulfonyl fluoride, 1 mM benzamidine, 5  $\mu$ M leupeptin and 1 mg/ml of egg trypsin inhibitor. The tissue was homogenized and a microsomal pellet was obtained after two differential centrifugation steps. The resulting microsomal pellet was resuspended in homogenization

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media and loaded onto two successive discontinuous sucrose density gradients. These gradient-purified CVs were chromatographed twice over a Sephacryl S-1000 gel filtration column.<sup>20</sup> Optical density at 280 nm of the material eluting from the column was determined using a Beckman spectrophotometer.<sup>2</sup> Coated vesicles were used immediately for assay or, when indicated, stored at 4°C for 48-72 hours.

**Phosphodiesterase Assay:** We used the isotopic method involving the column separation procedure.<sup>21</sup> The final reaction mixture consisted of 40 mM Tris-HCl, pH 7.4, 5 mM 2-mercaptoethanol, 5mM MgSO<sub>4</sub> and about 10<sup>5</sup> counts per minute of <sup>3</sup>H-cAMP per assay tube. The cAMP and cGMP hydrolysis dose-response curves, were obtained by isotopic dilutions using 0.5-200 uM cAMP. Non-specific hydrolysis was determined on parallel blanks containing 10 mM theophylline, 1 mM IBMX or by boiling the tissue prior to assay. Final assay volume was 400 ul and contained 5-25 ug of tissue protein, a range wherein hydrolysis was a linear function of tissue added. Reactions were started by mixing all reagents in an ice bath, rapidly equilibrating them to 30°C and incubating them for 10 minutes. The reaction was stopped by placing the tubes in boiling water. Tubes were cooled immediately in an ice bath and 100 ul of 5'nucleotidase (2.5 units/ml) from *Crotalus atrox* (Sigma, Co.) added. The tubes were incubated for 10 minutes at 30°C, then placed in an ice bath and 1 ml of methanol added to each tube. Tube contents were separated over an AGIX8 anion-exchange resin. The column eluate was collected in scintillation vials and 10 ml of Scintiverse added to each. Counting was performed at about 40% efficiency.

**Data Analysis:** Dose-response curves were analyzed using the Logistic program in Prophet. The logistic function is equivalent to the Hill equation<sup>22</sup> and yields apparent K<sub>m</sub> and Hill slope values from the experimental data. The simulation curves were obtained after their solution with the indicated parameter values (Figures 2, 3, 4). Their apparent Hill slopes and K<sub>m</sub> values were obtained by fitting the logistic function to the simulation curves (Figures 3 and 4).

**Material:** All reagents were of analytical grade I. Cyclic -AMP, cGMP, bovine serum albumin, N-tris (hydroxymethyl) methyl-2-aminoethane sulfonic acid (Tris), morpholinoethanesulfonic acid (MES), 5' nucleotidase were from Sigma Co., St. Louis, Missouri. Tritiated cAMP and cGMP were from New England Nuclear, Boston, Massachusetts. The AGI-X8 resin was from BioRad Co., Rockville Centre, New York. Methanol, dimethyl sulfoxide and Scintiverse were from Fisher Co., Springfield, New Jersey. The Sephacryl S-1000 gel filtration column was from Pharmacia (Sweden).

## Results

### Equilibrium kinetics behavior of the brain CV type II PDE

The kinetic parameters for cAMP as substrate for the PDE activity associated with bovine brain CVs are shown in Table I. The enzyme hydrolyzes cAMP with an apparent K<sub>m</sub> of 22 uM.<sup>2</sup> The kinetics of hydrolysis also suggest positive cooperativity, as revealed by Hill slope values greater than one for cAMP. Activation of cAMP

hydrolysis by cGMP, lowers the K<sub>m</sub> of the enzyme for cAMP, returns the Hill slope value to unity, with no significant changes in the V<sub>max</sub> of the enzyme produced. In addition, catalysis of both cyclic nucleotides still occurs following an extensive decrease (200%) of the cGMP-activation capacity after prolonged storage (after 48-72 hours) of the CVs enzyme at 4°C (Figure 1, Table I). The loss of activation by cGMP was accompanied also by a change in the kinetic behavior of the enzyme. This change culminates with an increase in apparent K<sub>m</sub> values and a return of the Hill slope to a value approaching one.

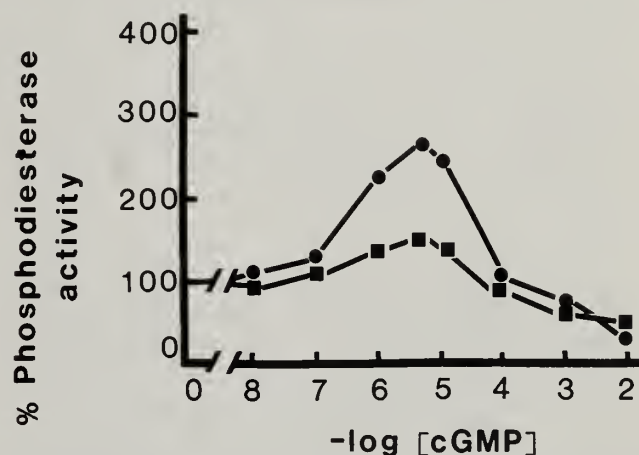


Figure 1. Effect of cGMP on the hydrolysis of cAMP by fresh (●) and stored (■) CVs. The maximal level of stimulation by cGMP in the aged, stored preparations was less than 50%.

Table I

Summary of kinetic parameters for the hydrolysis of cAMP by the brain CV type II PDE activity as a function of the activation capacity by cGMP

	Apparent K <sub>m</sub> (uM)	V <sub>max</sub>	Slope	N
Activation by cGMP				
CV (control)	20	2.1	1.5	(3)
CV + 5 uM cGMP	11	2.3	1.05	(3)
After loss of activation by cGMP				
CV (control)	22	3.2	1.5	(5)
CV poor cGMP activation*	37	3.4	1.08	(4)

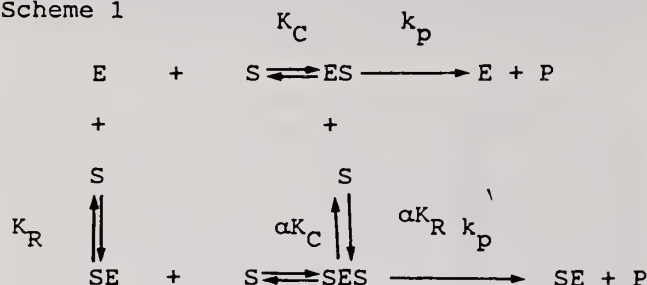
V<sub>max</sub>=nmol/minute/mg  
Slope=Hill slope  
N=number of experiments  
\*=see figure 1 and Methods.

### Equilibrium Kinetics model for the Brain CV type II PDE

In addition to the classical models of positive cooperativity, various kinetic schemes can account for Hill slopes higher than one as those obtained in our determinations. Substrate activation schemes are examples of these and are directly pertinent to the case of type II enzymes, since a substrate (cGMP) also activates the enzyme. Substrate activation, may or may not be a requirement for catalysis, essential versus non-essential.<sup>22</sup> Since cyclic nucleotide

hydrolysis takes place after considerable loss of the activation capacity we propose that the CV type II PDE enzyme fits a case of non-essential substrate activation. Assuming the presence of a regulatory (allosteric) site, and that changes in the apparent  $K_m$  of the enzyme are determined by an arbitrarily assigned activation factor (called alpha,  $a$ ), the following equilibrium kinetics scheme is proposed:

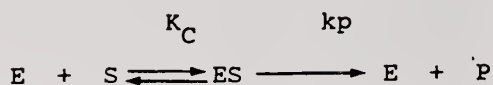
Scheme 1



where E=enzyme with a regulatory (R) and catalytic (C) site, S=substrate (cAMP or cGMP), ES=enzyme-substrate complex at the catalytic site, SE=substrate-enzyme complex at the regulatory site, SES=ternary complex where substrate is bound to the regulatory and catalytic sites,  $K_C$ =intrinsic dissociation constant of the substrate for the catalytic site (unactivated state),  $K_R$ =intrinsic dissociation constant of the substrate for the regulatory-activation site,  $K_p$ =catalytic rate constant, P=product (AMP or GMP) and  $a$ =(activation factor) factor by which the apparent affinity of the catalytic site for the substrate is changed after occupancy of the regulatory-activation site. This regulatory site is regarded as an effector or allosteric site<sup>22</sup> recognized by the substrates and other effectors as well. Occupancy by cGMP or other activators of this regulatory site (SE) leads to an activated state.

The model predicts that when the enzyme loses its activation capacity or regulatory site, the kinetic scheme reduces to:

Scheme 2



Therefore, under this condition the curves for the hydrolysis of cyclic nucleotides will be of a simple Michaelis-Menten kinetic behavior.

A simple equilibrium kinetic behavior is also predicted for the experimental scenario where saturating amounts of activators are present, i.e. the cAMP hydrolysis dose-response curves in the presence of 5  $\mu\text{M}$  cGMP. Again, the equilibrium kinetic scheme is reduced to:

Scheme 3



### Application of the model to the brain CV and other type II PDE

Both of the conditions for the application of schemes 2 and 3 are met by type II PDEs of rat liver cytosol and CVs.<sup>2, 4, 15</sup> As stated above, following loss of the activation capacity by cGMP the Hill slope returns to one and the apparent  $K_m$  value for the hydrolysis of cAMP is increased (Table I).<sup>2, 4, 15</sup> Therefore, under the experimental conditions of scheme 2 we can assume that the apparent  $K_m$  value approaches the real  $K_m$  of each cyclic nucleotide. The  $K_C$  value for cAMP is 38  $\mu\text{M}$  (Tables I). This is an approximation since the enzyme still displayed 10-50% residual activation capacities, for cAMP we arbitrarily fixed the  $K_C$  value to 30  $\mu\text{M}$  for the simulation analysis of figures 2-4.

Meanwhile, when the model is reduced to scheme 3, that is in the presence of saturating amount of activator(s): apparent  $K_m = aK_C$ .

In Table I we show the  $K_C$  value of the CV enzyme to be approximately 10  $\mu\text{M}$ . Yet, this value must be corrected for the possible amount of cGMP (5  $\mu\text{M}$ ) binding to the catalytic site.<sup>22</sup> The apparent  $K_m$  for this experiments is:

$$\text{apparent } K_m = aK_C \left( 1 + \frac{[\text{cGMP}]}{K_G} \right)$$

Using  $K_C$  (for cAMP)=40  $\mu\text{M}$ , [cGMP]=5  $\mu\text{M}$ ,  $K_G$  for cGMP=10  $\mu\text{M}$  (unpublished results), and an apparent  $K_m$  for cAMP (in the presence of cGMP) of 10  $\mu\text{M}$  (see Table I). From these calculations we can attempt an approximation of the activation factor ( $a$ ) value for cAMP. The resulting value is of 0.16. This low value of for cAMP is also consistent with its dose-response curves having Hill slopes in the vicinity of 1.5 (Figure 4). From the simulation analysis it can be seen that only alpha values lower than 0.25 will yield Hill slopes close to 1.5 (Figures 2 and 4).

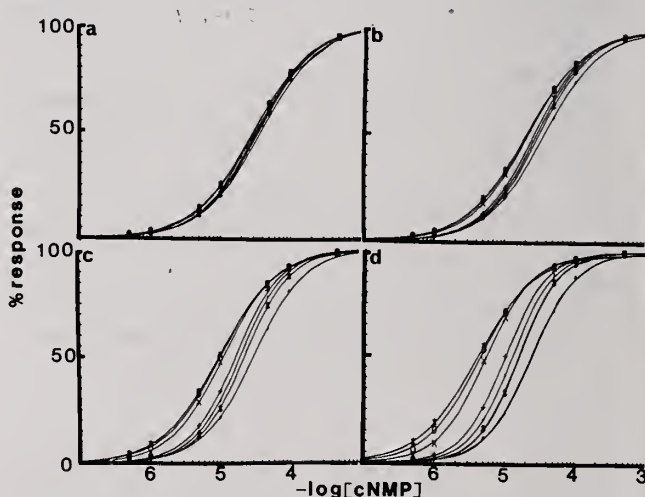


Figure 2. Simulation curves obtained from the steady-state solution of the kinetic model. The value of  $a$  was set to 1 (panel a), 0.75 (panel b), 0.25 (panel c) and 0.1 (panel d). In each panel the curves from right to left represent increasing  $K_C/K_R$  ratios: 0.1, 0.5, 1, 2, 20, 80 and 400, respectively. They all represent normalized dose-response curves since no significant changes are seen in the  $V_{max}$  after the stimulation or aging of the enzyme.<sup>2, 6, 13, 14, 15</sup>



The other factor contributing to changes in the observed slopes and  $K_m$  values is the relative affinity of each substrate for the catalytic and regulatory sites of the enzyme, the  $K_C/K_R$  ratio. Using the above estimates the  $K_R$  value for cAMP can be calculated to be of 137  $\mu\text{M}$ , and a resulting  $K_C/K_R$  of 0.18. In Figures 2 and 3 we depict that low  $K_C/K_R$  ratios shift the simulation hydrolysis dose response curves to the right.

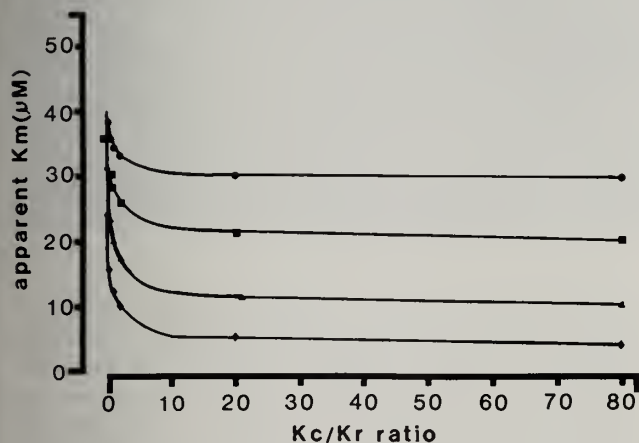


Figure 3. Variations in apparent  $K_m$  as a function of  $a$  and the  $K_C/K_R$  ratio. The values are from the simulation curves in Figure 2. Various  $a$  values were used: 1 (●), 0.75 (■), 0.25 (▲) and 0.1 (◆).

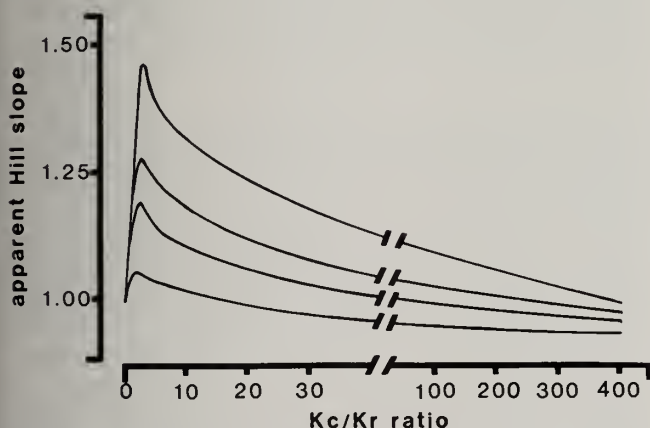


Figure 4. Variations in the apparent Hill slope as a function of the activation factor  $a$  and the  $K_C/K_R$  ratio. Values were derived from the analysis of the simulation curves in Figure 2. The curves from top to bottom are representative of increasing values of  $a$ , 0.1, 0.25, 0.75 and 1, respectively.

### Discussion

Among the cGMP-stimulated PDE enzyme systems, the best characterized is the soluble form of the enzyme from rat liver.<sup>8, 9, 15, 16, 23</sup> This analysis of the CV type II PDE represents one of the very few for particulate type II PDEs, since these have not been as thoroughly characterized and kinetically analyzed. The particulate nature of the type II PDE of CVs leads us to consider it as an ideal novel system to study particulate-bound type II PDE. The presence of catalysis after loss of activation capacity suggests that the type II enzyme of CVs fits the nonessential activation type and that occupancy of the

regulatory and catalytic sites is random.<sup>22</sup> Thus, the CV type II PDE represents one of the few examples of nonessential random substrate activation.<sup>22</sup>

The experimentally determined molecular interactions reveal that the substrate cGMP is a positive allosteric modulator of the enzyme. In the CV type II PDE, as well as in other cGMP-stimulated enzymes, the Hill slope value of the cAMP dose-response curves done in the presence of cGMP and other activators return to a value close to one.<sup>2, 4, 15</sup> In all cases the  $V_{max}$  did not significantly change and the apparent  $K_m$  decreased.<sup>2, 4, 15, 22</sup> The absence of significant changes in the  $V_{max}$  of the enzyme during activation or loss of the activation capacity by cGMP also provides insights into the mechanisms of the enzyme. First, it means that activation of the enzyme by substrate only produces changes in the apparent affinity of the enzyme for the substrate at the catalytic site. And second, that no changes in the catalytic rate ( $K_p$ ) of the reaction take place during substrate (cGMP) activation. This lack of change in  $V_{max}$  contrasts with those changes seen during activation of type I enzymes by calmodulin. It can be inferred, therefore that activation of type II PDE by cGMP or its analogues<sup>2, 15, 16</sup> does not release an inhibitory influence imposed by the regulatory domain on the catalytic function of the enzyme. These observations hold true for both cytosolic and particulate type II PDEs.

The analysis of the various kinetic parameters also yielded valuable information. Considering the fact that the dose-response curve for cAMP lies to the right of the curve for cGMP, suggests that a larger  $K_C/K_R$  ratio applies for cGMP.<sup>2, 4, 15</sup> This implies a higher affinity for the regulatory site for cGMP, which may explain why cGMP activates cAMP hydrolysis and not the opposite occurs. In contrast, the higher Hill slope values for cAMP can be attributed to its lower  $a$  value ( $a=0.16$  for cAMP). If similar calculations are attempted for cGMP (unpublished results) we obtain an activation factor and  $K_C/K_R$  ratio of 0.38 and 13, respectively. These relatively high values of  $a$  and  $K_C/K_R$  for cGMP are consistent and help to explain the lower apparent  $K_m$  and Hill slope values reported for this cyclic nucleotide with some type II PDE analyzed.<sup>2, 10, 15</sup>

Previous studies have shown that inhibition of the type II PDE of CV and other systems by different inhibitors display Hill slopes different from one.<sup>2, 8, 9, 23</sup> These shallow Hill slopes could be related to a heterogeneity of binding affinities or activation capacity of these inhibitors for the catalytic and regulatory domains of type II PDEs. For instance, IBMX and papaverine are not activators of the CV PDE<sup>2</sup> but they activate the cytosolic liver enzyme.<sup>2, 8, 9, 23</sup> Understanding the mechanistic aspects of the family of PDE bears potential clinical relevance since these enzymes are the targets of action for drugs used in the management of asthma and cardiovascular diseases.

At present, the significance of the presence of a type II PDE in the CV organelle can only be estimated indirectly. One likely aspect is related to the organelle recycling capacity of lipids and proteins from the plasma membrane and/or their replenishment. More important, however, is the possibility that the PDE plays a critical

role in the internal specific functions of CVs related to, a) the transport of cargo molecules to and from the plasma membrane or from the Golgi apparatus, and b) acidification of the internal milieu of the CV for segregation of internalized ligand and receptor molecules.

### Acknowledgements

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# REVIEW ARTICLES

## Prognostic Factors in Patients with IVDA and Bacteremia

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Robert Hunter-Mellado, MD

**Abstract:** The medical records of all the patients with bacteremia and recent use of illicit intravenous drugs admitted to Hospital Universitario Ramón Ruíz Arnau from January 1, 1988 to June 30, 1989 were reviewed. It consisted of 28 records, 21 of which were male patients and 7 females. The mortality rate among these patients was 46%. *Staphylococcus aureus* was the most common pathogen recovered from blood cultures. All the *S. aureus* were methicillin sensitive. The presence of clinical sepsis, a low Karnofsky performance status at the time of admission and multiorgan abnormalities were the most important prognostic factors that determined outcome in these patients.

Bacteremia has been reported to occur in up to 15% of patients who actively use illicit intravenous drugs.<sup>1</sup> The most common source of infection found in intravenous drug abusers (IVDA) is soft tissue infection from contaminated needle punctures. The infectious complications from bacteremia in IVDA include bacterial endocarditis,<sup>2</sup> septic emboli from infected cardiac valves<sup>1, 2</sup> or septic thrombophlebitis, meningitis and osteomyelitis.<sup>1</sup>

The treatment of infectious complications in this population of patients is complex for a variety of reasons. First, the clinical features of infections in IVDA are usually more subtle than in the general population.<sup>3, 4</sup> There is a high frequency of non-prescribed antibiotics usage obscuring the clinical picture. The elevated incidence of methicillin resistant *S. aureus*, gram negative bacteria and polymicrobial infections in IVDA are important factors to recognize. There is the presence of febrile reactions due to the injection of foreign material at the time of illicit drug administration.<sup>1</sup> Furthermore, these patients have a high incidence of viral infections which are transmitted through blood such as cytomegalovirus (CMV), hepatitis and Human Immunodeficiency Virus (HIV).

The advent of the HIV epidemic and the development of the Acquired Immunodeficiency Syndrome (AIDS) in a large number of HIV infected patients, has further augmented the complexity of infections in this population of patients.<sup>5</sup> Clinicians need to include opportunistic protozoan, fungal and bacterial infections and autoimmune diseases in the evaluation of a febrile patient who actively uses intravenous drugs. Furthermore, defining the etiology of the infectious processes in patients with AIDS requires invasive procedures of varying degrees of complexity and sophistication. The management of these patients is particularly difficult in institutions that lack the necessary facilities to perform these studies.

We decided to review, in a retrospective manner, the prognostic factors that influence the outcome of patients with IVDA and bacteremia at our university hospital.

### Material and Methods

We reviewed all the medical records of patients admitted to the Hospital Universitario Ramón Ruíz Arnau (HURRA) who had three positive consecutive blood cultures with the same organism. The records were reviewed for documentation of current use of illicit intravenous drugs at the time of admission. The records of patients with bacteremia and IVDA are the subject of this report.

The medical records were reviewed for the site of origin of the bacteremia, type of bacteria and antibiotic sensitivities, presence of signs and symptoms of sepsis, and for the presence of organ dysfunction in particular hematologic, CNS, cardiac, pulmonary, renal and hepatic abnormalities.

Sepsis was defined as the presence of bacteremia and at least 3 of the following features: fever, tachycardia, chills, tachypnea, hypotension, leukocytosis or leukopenia. The presence of organ abnormalities was defined for each system according to pre-set criterias. Hematologic abnormalities were defined as any abnormal value for WBC counts, hemoglobin, hematocrit, platelet count, PT and PTT. Central nervous system dysfunction was defined as the presence of changes in the level of consciousness in association with the presence of physical findings sugges-

tive of meningitis and/or a structural brain lesion. Cardiac dysfunction was considered as the presence of signs and symptoms of CHF, or the presence of electrocardiographical abnormalities in the conduction system. Bacterial endocarditis was defined as definite when the patient had evidence of valvular infection at the time of autopsy or abnormal M-mode or 2-D-Echocardiogram along with a heart murmur. Bacterial endocarditis was defined as probable when the patient had a heart murmur and embolic phenomena highly suggestive of septic embolization. Pulmonary involvement was defined by the presence of acute pneumonic infiltrate(s) in chest radiographs and the presence of hypoxia ( $PO_2 < 70$  at room air;  $< 90$  with oxygen supplementation). Renal dysfunction was defined as a serum creatinine  $> 1.5$  mg/dl in females and  $> 1.8$  mg/dl in males with or without the presence of hematuria ( $> 10$  RBC/hpf) or proteinuria ( $> 100$  mgs/dl) in a routine urinalysis. Hepatic dysfunction was defined as an elevation greater than 2 times normal for AST, ALT and alkaline phosphatase, low albumin ( $< 2.5$  gm %) and elevated bilirubin ( $> 3$  mg%).

Finally, the performance status of the patient at the time of admission was calculated, using the Karnofsky scale.

Positive cultures obtained from different sources in an individual patient were compared for organism identification and pattern of antibiotic sensitivity. Antibiotic regimens prescribed at the time of admission and revisions of the antibiotic therapy used in each patient were recorded and evaluated.

Statistical analysis was done with Chi square test.

### Results

We reviewed 170 medical records of patients who were admitted to the Department of Medicine from January 1, 1988 to June 30, 1989, and had culture proven bacteremia. Of these, 28 had documentation in the medical record of recent use of illicit intravenous drugs.

In Table I a comparison between age and sex of patients discharged alive and those who died is made. The average age of the patients who died during their admission or were discharged home was similar. A total of 13 patients died for a 46% mortality rate. The difference in mortality in males compared to females was not statistically significant.

Table I - Identification of Patients

		Mean Age (Y)		Range		Mortality Percent	
		Alive	Dead	Alive	Dead	No. PTS	Mortality
	Num.					13	46%
Men	21	35	33	26-50	26-45	9	42%
Women	7	31	33	28-36	26-48	4	57%

The organisms recovered from cultures is reported in Table II. *Staphylococcus aureus* was the organism most commonly isolated. There were 2 patients with polymicrobial bacteremia, 3 patients with *Salmonella* and 1 patient with *Pseudomonas*. The source of the bacteremia is believed to be the skin secondary to IV puncture in all

Table II - Identification of Bacteria

Number	Percent	Bacteria	Source of Positive Culture	Primary Site of Infection
17	61%	<i>S. aureus</i>	Blood	Skin
2	7%	<i>S. aureus</i>	*Blood/CNS	Skin
2	6%	Enterococci group D	Blood	Skin
		<i>S. aureus</i>		
3	11%	<i>Salmonella</i> group D	*Blood/GI	GI tract
3	11%	Unclassified	Blood	Skin
1	30%	<i>Pseudomona</i>	*Blood/CNS	Skin

\*Sensitivity patterns to antibiotics in both sources was identical

patients except the three patients with *Salmonella*.

The three patients with *Salmonella* bacteremia also had the same organism with identical antibiotic sensitivities isolated from stool. Three patients who had positive blood cultures (2 with *S. aureus* and 1 with *Pseudomona*), also had a positive culture from cerebrospinal fluid. In all instances the same bacteria with an identical sensitivity pattern was isolated from both sites. All isolates of *S. aureus* were methicillin sensitive organisms.

Table III describes the Karnofsky performance status at the time of admission. The performance status was 62% in those patients discharged alive as compared to 31.5% in patients who died. A performance status greater than 60% correlated with 100% survival and of 39% or lower with 100% mortality. Variable outcomes are seen between 40-59% performance status.

Table III - Performance Status

PS	Alive	Dead	Mortality
10-19	--	1	100%
20-29	--	4	100%
30-39	--	3	100%
40-49	3	2	40%
50-59	2	3	60%
60-69	5	--	0
70-79	1	--	0
80-90	4	--	0
Average	31.5	62	46%

The number of patients with target organ dysfunction as it relates to mortality is presented in table IV. Cardiac involvement was similar in both groups, while gastrointestinal abnormalities were seen only in patients with a positive outcome. Furthermore, patients who died during their hospitalization had a much higher presence of clinical sepsis accompanying the bacteremia than those who lived. Lung, renal and hepatic dysfunction was more often seen in patients with a negative outcome.

Table IV - Number of Individuals (%) with Individual Organ Involvement and Clinical Sepsis

	Num.	Sepsis	Lung	Hepatic	GI	CNS	Renal	Heart
Alive	15	31.2%	6.6%	7%	20%	13.2%	13%	60%
Dead	13	85%	69%	30%	0%	30%	30%	69%



All patients were stratified in relation to the number of systems involved at the time of admission (Table V). In patients with two or more individual target organ dysfunction a mortality of 13 of 20 (65%) was seen as compared to 0/8 (0%) in patients with one or no target organ dysfunction.

Table V - Multiorgan Abnormalities

	Number Sites of Disease		
	0	1	2
Alive	3	5	7
Dead	0	0	13

We have analysed the antibiotic regimen selection on admission for all patients who died in relation to the organism isolated in cultures. The selection of antibiotics was found to be adequate in 7 patients, partially adequate in 2, inadequate in 2 (#2,16) and unable to determine in 2 (#5,9). Subsequent modification of antibiotics used in these patients often occurred with eventual adequate coverage in all but one patient (Table VI).

It has been reported that up to 53% of IVDA patients with their first episode of infective endocarditis (IE) succumb in their first admission.<sup>2</sup> This is believed to be related to rapid destruction of normal cardiac valves by the bacteria. In our patient population we identified 18 patients with infective endocarditis (IE) with a 50% mortality. Sixteen patients had IE limited to the tricuspid valve, one patient had tricuspid and aortic involvement, and one patient had tricuspid and mitral vegetations. Our mortality rate is similar to that reported in other studies. One of our patients developed congestive heart failure which was quickly controlled with medical treatment. We could not correlate mortality with degree of cardiac dysfunction in the remaining patients with IE.

In this study the major prognostic factors that determined outcome were a low Karnofsky performance status at the time of admission, presence of clinical sepsis and multiorgan involvement. The low Karnofsky performance status and the higher incidence of clinical sepsis in the group of dead patients was statistically significant when compared to the group of survivors.

Table VI - Admission and Revision of Antibiotics Used in Patients with a Negative Outcome

PT.	Bacteria	Antibiotics on Admission	Day of Review	Antibiotic Modification	Death (Day)
# 2	Staph.aureus	Septa	8	Nafcillin, Garamycin	366
# 5	Unclassified	Nafcillin, Garamycin	--	--	2
# 6	Staph.aureus	Septa, Erytromycin	3	Nafcillin, Gramycin	8
# 8	Pseudomona aeruginosa	Penicillin, Garamycin	1	Tazicef, Amikin	4
# 9	Unclassified Gram (-) Bacilli	Septa, Erytromycin	--	--	4
#13	Staph.aureus	Nafcillin	1	Vancomycin, Garamycin	3
#14	Staph.aureus	Nafcillin	3	Garamycin, Nafcillin	41
#16	Staph.aureus	Penicillin Garamycin	--	--	5
#17	Staph.aureus	Septa, Erytromycin	--	--	5
		Mezlocillin	--	--	5
#20	Staph.aureus	Nafcillin, Garamycin	8	Vancomycin	20
#18	Staph.aureus	Nafcillin, Erytromycin	--	--	0.5
		Septa			
#28	Staph.aureus	Nafcillin, Garamycin	--	--	3
#27	Staph.aureus	Nafcillin, Amikin	15	Vancomycin	31

### Discussion

Bacteremia remains a common finding in patients with IVDA. It has been recently reported that a poor outcome in some patients with IVDA and bacteremia may be related to an incorrect initial antibiotic regimen. This is mentioned due to a significant number of *S. aureus* isolates which are Methicillin resistant or that patients may have a higher incidence of polymicrobial or *Pseudomona* bacteremia than in the past. In this series all *S. aureus* isolates found were methicillin sensitive. In addition there is a lower number of polymicrobial and *Pseudomona* related bacteremia than in other reports. The empiric antibiotic selection at the time of admission was adequate in most of the patients. We therefore do not feel that these factors are critical in defining the poor prognosis of these patients.

The data presented shows that patients who eventually die have a higher incidence of central nervous system (CNS), renal, pulmonary and hepatic involvement. In addition patients with the syndrome of clinical sepsis and 2 or more organ dysfunction fared significantly worse.

The management of infectious complications in patients with IVDA has been complicated by the advent of the AIDS epidemic.<sup>5</sup> With this epidemic a new dimension of infectious complications need to be considered in the IVDA patient.<sup>5</sup> In this report all of the patients were HIV positive. In the patients with concomitant CNS or gastrointestinal involvement it appears that this was related to the bacteremic process since the same organism with identical antibiotic sensitivity pattern was found. Cardiac involvement was in all instances related to infective endocarditis. Renal and hepatic involvement

was believed to be either secondary to a viral infection acquired through IVDA or related to the use of illicit drugs.

The most difficult organ to evaluate in terms of infectious complications resulting from bacteremia was the lung. Of the nine patients with pulmonary dysfunction who died, eight had documented endocarditis with the chest radiograph highly suggestive of septic emboli. In the remaining patient an interstitial process was present compatible with *P. carinii*. In the patients who underwent autopsy, no evidence of opportunistic infections or malignant processes were found.

In this report we have analysed the natural history of patients who are IVDA with bacteremia. Our data suggests that admission performance status, the presence of clinical sepsis and multiorgan involvement is of prognostic importance in these patients.

#### Acknowledgement

We are grateful for the secretarial help of Ana M. Meléndez Castro.

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## YOCON® YOHIMBINE HCl

**Description:** Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

**Action:** Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

**Indications:** Yocon® is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

**Contraindications:** Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

**Warning:** Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

**Adverse Reactions:** Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.<sup>1,2</sup> Also dizziness, headache, skin flushing reported when used orally.<sup>1,3</sup>

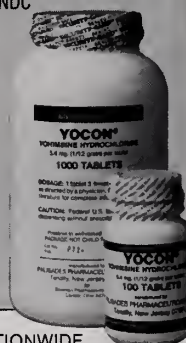
**Dosage and Administration:** Experimental dosage reported in treatment of erectile impotence.<sup>1,3,4</sup> 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.<sup>3</sup>

**How Supplied:** Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

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# Squamous Cell Carcinoma of the Penis

R. Hunter-Mellado, MD  
P. Rodríguez

**Abstract:** Squamous cell carcinoma of the penis (CA Penis) is not a rare disease in P.R. We have reviewed all cases of CA penis diagnosed in our institution from Jan. 79 - Jan. 89. Pathology and hospital records were audited. The survival data on all patients was updated via telephone or record review up to May 89. A total of 18 pts were seen in the last decade. Of these 11, (61%) were seen in the last four years. Four of 18 patients were excluded from analysis due to lack of staging and therapy data. The median age 54.9 y (range 23-82y). The following risk factors were identified: phimosis 12/14 (86%)  $p=.05$ , leukoplakia 8/14 (57%); prior venereal disease 1/14 (7%). The primary lesion appeared in the prepuce 8/14 (57%) and glans 6/14 (43%). TNM staging was done in all pts. Most pts presented with T3 or T4 disease 10/14 (71%) and palpable regional adenopathy (N1-N3) 9/14 (64%). Of the nine pts with palpable adenopathy, in 5 (56%) microscopic malignant disease was confirmed. A correlation between T3 or T4 disease and the presence of palpable adenopathy was seen (80%). The Stage at diagnosis of the 14 pts: I: 0/14 (29%), II: 5/14 (7%), III: 3/14 (21%), IV: 6/14; (43%). All pts were treated with partial penectomy and 7/14 had unilateral or bilateral inguinal lymphadenectomy. Long term survivors (LTS), greater than 12 mo., were seen 3/4 pts with Stage II disease, 1/3 Stage III, and 2/5 in Stage IV. The most important prognostic factor for LTS was malignant involvement of regional lymph nodes with 0/5 in this group. In contrast with 6/9 LTS in pts without regional disease. These findings suggest that more intense therapy is needed for pts with documented regional lymph node metastasis.

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Squamous cell carcinoma of the penis is a relatively uncommon tumor in Puerto Rico. Nevertheless the incidence of this tumor is nearly four times higher in the island as compared to the continental United States. Squamous cell carcinoma is responsible for 1.8% of all neoplasia in men in Puerto Rico as compared to .4% in the continental United States.<sup>1, 2</sup>

The crude rate of this malignancy in Puerto Rico for the 1950-1960 period was 4.3 cases per 100,000 male population.<sup>3</sup> The crude rate in 1985 remains at 4 cases per 100,000.<sup>1</sup> The absence of a decline in the crude rate of a tumor which appear quite amenable to prevention via early circumcision has prompted us to review some of the features of the natural history of this tumor in our institution.

## Methods

All pathologic reports for the period between January 1979-January 1989 were reviewed. Patients with a diagnosis of Carcinoma of Penis were identified and the pathologic reports reviewed. The hospital medical records and the oncology division records of these patients were examined.

All patients were retrospectively re-staged according to the Tumor-Node-Metastatic (TNM) classification as proposed by the American Joint Committee (table I). The TNM classification was then used to uniformly establish a stage for each patient according to Jackson's criteria.<sup>4</sup> Stage I - Non Infiltrating Local Disease; Stage II - Advanced local disease but no nodal involvement; Stage III - Presence of unilateral nodal enlargement, Stage IV - Ulcerated or Fixation of regional lymph nodes.

Statistical analysis was done using the sign rank sum test.

Survival time was defined as time between initial diagnosis and death or last documented contact with the institution. Survival information was updated in all patients lost to follow by telephone communication.

Table 1 - Squamous Cell Carcinoma TNM Staging

T	N	M
T1 - tumor not more than 1 cm and superficial	N0 - No involvement of regional nodes	M0 - No metastasis
T2 - tumor greater than 1 cm and superficial	N1 - Enlargement single regional node	M1 - Extra nodal metastasis
T3 - Invasive tumor	N2 - Enlargement of single bilateral inguinal nodes or multiple unilateral nodes	
T4 - Invasive tumor to corpus, urethra, perineum	N3 - Fixation or ulceration of regional nodes	

## Results

A total of 18 patients with carcinoma of the penis were identified between January 1979 and January 1989. Of these 18 patients were diagnosed after 1985 (61%) and 7 (39%) prior to 1985. All had squamous cell carcinoma as the histology. Four of these patients were excluded from the staging and survival analysis due to the absence of the hospital medical record. The mean age at diagnosis was 54.9 years with a range between 23 - 82 years. Four of the 12 patients were younger than 39 years.

An attempt was made to establish the presence or absence of several presumptive risks factors for this neoplasia (table 2). Phimosis was present in 12 pts (85.7%) and leukoplakia was seen in 8 (57%). The former

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Table 2 - CA of Penis; Frequency of risk factors

Factor present	Yes		No		p. value**
	No. of cases (%)		No. of cases (%)		
Phimosis	12 (85.7)		2 (14.3)		P= .05
Leukoplakia	8 (57.1)		6 (42.9)		NS
Venereal Disease	1 (7.1)		13 (92.9)		p= .01

\*sign rank sum test

was statistically significant with a P value of .05. A history of prior venereal disease was not detected in the majority of patients. The primary site of the lesion was the prepuce in 8 (57%) and the glans in 6 (43%). All patients underwent either partial or total penectomy for control of the primary lesion, and seven patients underwent unilateral or bilateral inguinal node dissection for control of regional disease. An analysis between the degree of "T" lesion, the type of surgical therapy given and survival is presented in table 3. Most patients

Table 3 - CA Penis  
Distribution by "Tumor" and Relationship to  
Therapy and Disease Free Survival

Tumor	No pts	Therapy		Disease free survival (months)
		Local	Regional	
T1	0			
T2	4 (29%)	4	0	45+, 15+, 3+, 1
T3	6 (43%)	6	5	104+, 29+, 30, 14, 10, 8+
T4	4 (29%)	4	2	114+, 48+, 7, 6

presented with advanced primary disease with 10 of 14 (71%) individuals having T3 or T4 disease. In the survival analysis no reliable correlation with predictive value was found between the T stage and the number of patients with disease free survival beyond 12 months. In patients with a minimum follow up of 12 months the survival was 66% for T2, 40% for T3 and 50% for T4. A correlation between tumor (T) and palpable inguinal adenopathy is made in table 4. All patients with regional palpable adenopathy underwent lymph node dissection with pathologic examination of the specimen. The number of patients with histologic confirmation of tumor is also included in table 4. An association between advanced primary disease and the presence of palpable inguinal adenopathy was seen. Of the 9 patients with palpable adenopathy 8 had T3 or T4 disease (89%). Histologic evaluation confirmed the presence of metastatic disease in 5 of these 9 patients (56%).

Table 4 - CA Penis

Relationship of "Tumor" and malignant nodal extension		
Tumor	Pts. with Adenopathy	Pts. with malignant extension
T2	1	0
T3 + T4	8	5
Total	9 (64%)	5 (36%)

A comparison between the node (N) status of these patients as determined on clinical grounds and the presence of pathologically confirmed metastatic disease is seen in table 5. A total of nine patients had clinical N2 or N3 disease, pathologic confirmation of malignant disease was established in 5 of these patients (56%). An analysis of survival and stage of the disease at diagnosis is presented in table 6. All patients were staged according to Jackson's criteria. The stage of presentation correlated with outcome with 4 of 5 (80%) patients remaining alive and free of disease in stages I and II as compared to 3 of 9 (33%) in stages III and IV. In two of the patients reported follow-up was less than 1 year. These patients remain free of disease as of October 1989.

Table 5 - CA of Penis:  
Comparison of clinical vs. Pathological adenopathy by node classification

Nx	Adenopathy	
	Clinical (%)	Pathologic (%)
N-0	5 (35.7)	0 (0)
N-1	0 (0)	0 (0)
N-2	7 (50)	3 (43)
N-3	2 (14.2)	2 (100)
Total	9 (64.2)	5 (56)

Table 6 - CA Penis

Distribution and Disease Free survival by Stage of Disease

Stage	No. Pts.	Disease Free Survival (months)
I	0	-
II	5 (36%)	1, 3+, 15+, 43+, 104+
III	3 (21%)	14, 30, 29+
IV	6 (43%)	6, 7, 18, 8+, 48+, 114+

We have attempted to establish a correlation between disease free survival and the degree of the primary lesion (T), the regional nodal status (N) and the overall stage of the disease as defined by Jackson's criteria. In general the T3 and T4 disease had poorer survival than those with T2 disease. On the other hand the presence of T3 or T4 disease was not incompatible with long term survival.

Palpable regional adenopathy was detected in 9 patients, 8 of which had advanced local disease in the primary lesion (T3, T4 disease). It is important to mention that in only 5 of these 9 patients metastatic disease was confirmed after histologic examination of the lymph node specimen. In the remaining 4 patients reactive hyperplasia was the cause of the nodal enlargement. The observation that the presence of palpable regional adenopathy often will not be related to metastatic disease has been previously reported.<sup>4, 5</sup> Hanash has reported that 58% of their patients with palpable adenopathy will be free of metastasis.<sup>4</sup> In 1986 Scott reported similar findings with a 50% discrepancy between clinical node enlargement and metastatic disease.<sup>5</sup>

The presence of nodal metastatic tumor was found to be an important predictor of survival. Four of the 5 patients with metastatic nodal disease have relapsed and



died of the disease as compared to 2 of 9 patients without microscopically confirmed metastatic tumor. It appears that more aggressive antineoplastic therapy is warranted for the group of patients with metastatic extension of the tumor.

A stronger correlation with survival was seen if patients were analyzed according to the presence or absence of histologically confirmed lymph node metastasis (table 7). Of the five patients with malignant regional node disease, four have died of active tumor (80%) as compared to 2 of 9 (22%) without regional disease.

Table 7 - CA Penis  
Disease Free Survival and Presence of Malignant Nodal Extension

Nodal Status	Histology	No. pts.	Disease free survival (months)
Non Enlarged	-	5	43+, 15+, 104+, 3+, 1
	Negative	4	29+, 30, 48+, 114+
Enlarged	Positive	5	14, 10, 6, 7, 8+

### Discussion

Squamous cell carcinoma of the penis remains an uncommon malignancy but clearly one that is suitable for early diagnosis and cure. In this paper we report the outcome of 14 patients with squamous cell carcinoma of penis, all which were diagnosed after 1979 and in which 43% eventually died of the tumor.

All patients in our series presented with primary lesions greater than 1 cm in its smallest dimension, and 10 of 14 had grossly advanced disease (T3 - T4 disease) The presence of phimosis was seen in 12 of 14 supporting the published reports that early circumcision may be of value in preventing this tumor.<sup>4</sup> The mean age of the patients was 59.5 y with 4 of 12 patients younger than 39 y. It is important to recognize that this disease affects patients in all adult age groups as seen in our experience in which patients in all decades of life between 20's and 80's were represented.

In this paper we have reviewed the experience at our institution with squamous cell Carcinoma of the Penis in the last decade. Carcinoma of penis continues to represent an important public health challenge in our island. Most patients present with neglected advanced disease at diagnosis and a substantial number of patients eventually succumb to the disease.

### Acknowledgement

We are grateful for the help of Eva Cesareo in preparing this manuscript.

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# Organophosphate Poisoning

Juan A. Rivera, MD  
Mayra Rivera, MD

**Abstract:** Organophosphate compounds insecticides are the most commonly associated with serious human toxicity. We reviewed the adult cases of organophosphate poisoning seen at HURRA from January 1986 to January 1990. We had 14 cases, all male patients. The most common mode of exposure was by ingestion in a suicidal attempt, (8/14 cases). The most common symptom observed was nausea (6/14 patients), and the most common sign was increased bronchial secretions (8/14 patients). Laboratory abnormalities were similar to those previously reported in the literature: leukocytosis (10/14 cases), hyperglycemia (5/14 cases) and hypokalemia (4/14 cases). Patients were treated following accepted guidelines. None of our patients developed seizures nor ventricular arrhythmias. One of our patients developed respiratory failure and required mechanical ventilation. Two patients developed pneumonic processes, requiring intravenous antibiotic therapy. The hospital stay of these two patients was prolonged (7 and 10 days respectively). For the other 12 patients, the hospital stay ranged from 2 to 4 days. We had no mortality in our series.

We were able to obtain follow-up interview by telephone with 10 of the 14 patients and we did not find any history of symptoms of delayed clinical toxicity.

Organophosphate compounds are the most popular of the chemical insecticides for home and agricultural use. They pose little environmental threat since they are rapidly hydrolyzed in the environment leaving minimal residues.

The existence of organophosphate compounds was known to man as far back as 1854. The first organophosphate compound developed was tetraethyl pyrophosphate (TEPP).<sup>1</sup> TEPP was developed by the Germans as an insecticide along with two other agents named "Tabun" and "Savin" developed as chemical warfare nerve agents. In view of the great toxicity of TEPP and its rapid inactivation in the presence of moisture this product was not commercially useful. In 1944 the development of parathion was announced. In that same decade the mechanism of toxicity of parathion was elucidated and atropine was discovered as an antidote.<sup>3</sup>

## Mechanism of Toxicity

Acetylcholine is the neurotransmitter present at the terminal ending of postganglionic parasympathetic nerves, at neuromuscular junctions and in the sym-

thetic and parasympathetic ganglion of the Autonomic Nervous System (Figure 1). After neurotransmission, Acetylcholine is hydrolysed into choline and acetic acid by acetylcholinesterases (Figure 2).

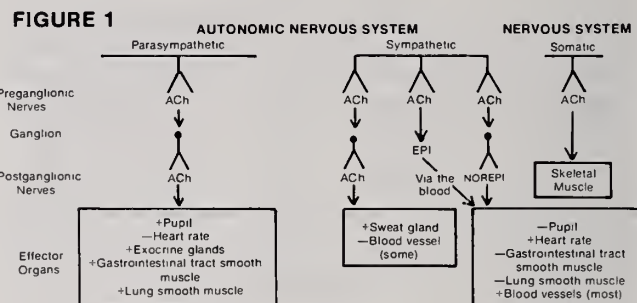


Figure 1. Schematic representation of the human peripheral nervous system (modified from Rymer WZ, 1981).

**FIGURE 2**

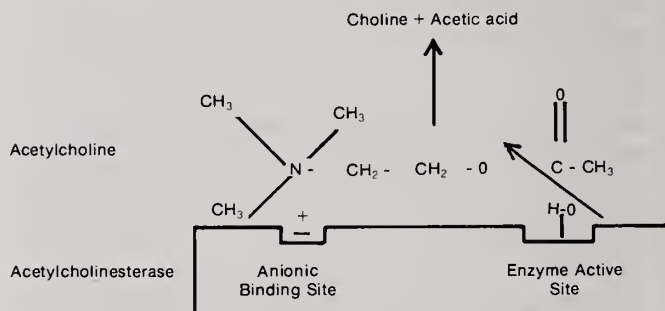


Figure 2. Schematic representation of hydrolysis of acetylcholine molecule by acetylcholinesterase. Anionic portion of molecule is attracted to anionic binding site, positioning molecule for hydrolysis at Enzyme Active Site. (Modified from reference 2).

Organophosphate compounds inhibit acetylcholinesterase by phosphorylating the enzyme and thus preventing the breakdown of acetylcholine and perpetuating nerve terminal stimulation (Figure 3).

Atropine competitively blocks the action of acetylcholine at the post-ganglionic parasympathetic nerves (muscarinic receptors), and thus decreasing the excessive stimulation at the parasympathetic nerves. Acetylcholine is also the neurotransmitter at neuromuscular junctions and in sympathetic and parasympathetic ganglia of the Autonomic Nervous System (nicotinic receptors) (Figure 1).



FIGURE 3

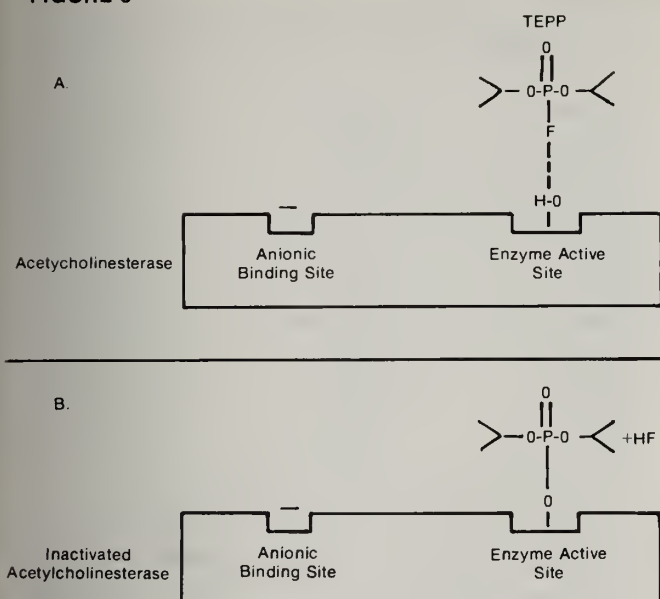


Figure 3. A. Interaction of the organophosphate TEPP and the active site of cholinesterase molecule.

A. Interaction of cholinesterase after covalent bonding of TEPP on active site. (Modified from reference 2).

Atropine does not exhibit significant activity in these receptors. Pralidoxime is the other important organophosphate antidote frequently used. This antidote reactivates acetylcholinesterase activity by breaking the phosphorus bonds induced by the organophosphate compounds (Figure 4).

FIGURE 4

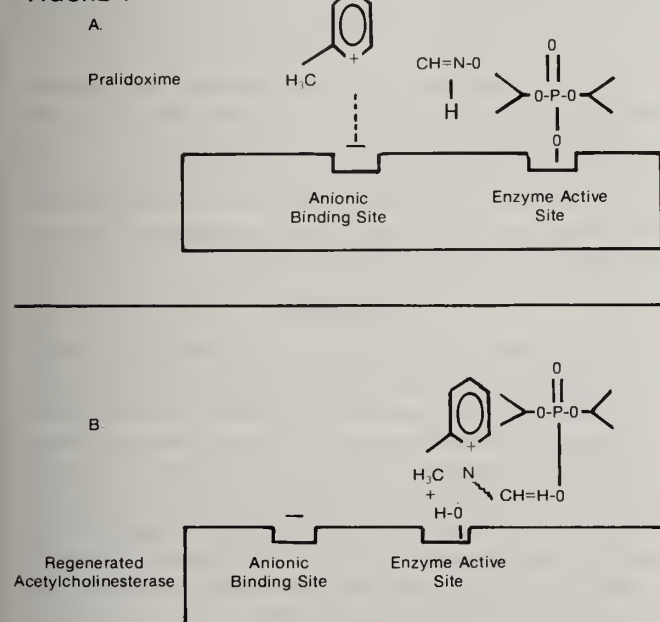


Figure 4. A. Interaction of pralidoxime and inactivated cholinesterase molecule. Pralidoxime is attracted to active site by electrostatic forces. B. When pralidoxime is close enough to the active site it binds with part of the organophosphate molecule, reactivating the cholinesterase. (Modified from reference 2).

Based on the distinct mechanism of action of pralidoxime and atropine on cholinesterase activity the concurrent use of both of these compounds is quite useful. Their pharmacologic effects are synergistic allowing the use of smaller doses of each of these compounds when used together. An additional advantage of pralidoxime is that it prevents the irreversible destruction of the phosphorylated cholinesterase which would take weeks to replace if the body had to manufacture new cholinesterase molecules.

### Methods

All patients cared for by the Department of Medicine admitted with a diagnosis of organophosphate poisoning between January 1986 to January 1990 were reviewed. A total of 14 patients were identified. All were males.

We reviewed the hospital charts of these patients, collected demographic data regarding age, sex, occupation, mode of exposure, signs and symptoms, laboratory data, therapy given, hospital stay, complications and outcome.

The information was updated by telephone communication with the patients and/or relatives. They were questioned about the development of recurrence of symptoms after discharge from the hospital and about the development of symptoms of peripheral neuropathy (i.e. burning or tingling of the legs or arms, weakness and difficulty walking).

### Results

Eight of the 14 patients (57%) ingested the compound in a suicidal attempt. Seven of these suicidal attempts were either alcoholics, intravenous drug abusers or carried a psychiatric diagnosis (Table I).

Twelve of the 14 patients presented with symptoms attributed to stimulation of the muscarinic receptor. Nausea was the most common symptom (6/14). Abdominal pain, salivation and vomiting, was found in 5/14 patients. The most common muscarinic sign was increased bronchial secretions (8/14), followed by miosis (7/14) (Table 2). The most common nicotinic sign was muscle fasciculations (5/14) followed by weakness (3/14). Alteration in general cerebral function was present in 5 patients and ranged from restlessness to coma (Table 2).

Laboratory abnormalities were similar to those previously reported in the literature (Table 3). The most common abnormality was leukocytosis with 10 of our patients presenting WBC counts of more than 10,000. Hyperglycemia (serum glucose > 120 mg/dl) was the second most common abnormality, seen in 5 patients. Four patients had serum potassium levels of less than 3.5 meq/l.

Patients who had ingested the compound orally underwent gastric lavage and activated charcoal therapy. Atropine was given in doses ranging from 0.4 mg to 33 mg. There was no documentation of the atropine dose in patient number 10. Pralidoxime was given to all patients except one, who only required a small dose of atropine (Table 4).

One patient, who was comatous on admission, developed respiratory failure, requiring mechanical ven-

Table 1 - Demographic Data

Pat No.	Age	Sex	Unverlying Psychiatric or Medical Condition	Occupation	Mode of
1	23	M	Depression	Salesman	suicidal attempt
2	166	M	None	farmer	accidental
3	31	M	Alcoholism	unemployed	suicidal attempt
4	61	M	Hypertension, Diabetes mellitus	farmer	accidental
5	26	M	I.V.D.A.	farmer	suicidal attempt
6	35	M	Alcoholism	retired (veteran)	suicidal attempt
7	37	M	Alcoholism	farmer	suicidal attempt
8	57	M	None	farmer	accidental
9	75	M	Alcoholism	retired	suicidal attempt
10	19	M	None	student	suicidal attempt
11	49	M	None	farmer	accidental
12	50	M	None	farmer	accidental
13	34	M	Manic-Depressive	construction worker	suicidal attempt
14	18	M	None	farmer	accidental

Table 2 - Clinical Manifestations

Pat. No.	Symptom	Signs	Mental Status
1	Salivation Abdominal Pain	Miosis, Bradicardia, Bronchial Secretions	Lethargic
2	Nausea, Vomiting		Alert
3	Salivation	Miosis, Brochial Secretions	Comatous
4	Salivation Lacrimation	Muscle Weakness	Confused
5		Muscle Fasciculations,	Restless
	Bronchial Secretions Loss of Consciousness Miosis		
6	Salivation	Bronchial Secretions, Diaphoresis, Bradicardia, Midriasis Muscle Fasciculations	Restless
7	Nausea, Vomiting	Muscle Fasciculations, Diarrhea Miosis, Bradicardia Muscle Weakness, Bronchial Secretions	Alert
8	Nausea, Vomiting Blurred Vision Lacrimation	Miosis, Muscle Fasciculations Bronchial Secretions	Alert
9	Salivation Abdominal Pain	Bronchial Secretions	Alert
10	Abdominal Pain		Alert
11	Nausea, Abdominal Pain, Vomiting	Miosis, Muscle Weakness	Alert
12		Miosis, Bradicardia, Muscle Fasciculations, Bronchial Secretions	Alert
13	Nausea, Vomiting Diarrhea	Bradycardia	Alert
14	Nausea, Abdominal Pain, Headache	Midriasis	Alert

Table 3 - Laboratory Findings (N/A = Results  
Not Found in Chart or Test Not Done)

No.	Count	Glucose	Pt.WBC Potassium	PaO2	PaCO2	Ph
1	13,700	N/A	3.2	113	33.4	7.37
2	N/A	N/A	N/A	N/A	N/A	N/A
3	19,800	121	4.1	56.1	41.2	7.34
4	10,000	224	3.2	N/A	N/A	N/A
5	17,700	81	3.8	53.2	38.2	7.34
6	17,200	119	3.2	51.9	27.2	7.40
7	20,700	83	4.1	180.3	37.1	7.32
8	17,100	155	2.9	123	37	7.41
9	8,200	N/A	3.5	128.5	35.7	7.46
10	12,900	97	N/A	N/A	N/A	
11	10,400	151	4.4	215	45.6	7.38
12	16,400	87	4.7	71	46.3	7.36
13	12,600	145	4.2	N/A	N/A	N/A
14	6,100	98	3.5	114	39.1	7.42

Table 4 - Management, Hospital Stay, and Complications

Pt. No.	Atropine (Dose in Milligrams)	Pralidoxime (Dose in Grams)	Acute Complications	Hospital Stay (Days)	Long-Term Complication (Recurrence of Symptoms and/or Peripheral Neuropathy)
1	33	2	None	3	None
2	1.8	2	None	2	None
3	2.5	3	Respiratory Failure	4	None
4	0.4	1	Pneumonia	7	None
5	22.4	10	Pneumonia	10	None
6	8	4	None	4	None
7	3.2	4	None	4	None
8	9.8	8	4	None	
9	1.4	3	None	3	None
10	—	1	None	3	None
11	7.6	4	None	3	None
12	11.4	1	None	3	None
13	0.8	--	None	3	None
14	1.6	3	None	2	None

tilation. Two patients developed pneumonia requiring antibiotics for 7 and 10 days respectively. In most patients the hospital stay ranged from 2 to 4 days. We had no mortality in our series.

Ten patients were interviewed over the telephone. All ten denied recurrence of symptoms suggestive of toxicity or of peripheral neuropathy (Table 4).

### Discussion

Organophosphate compounds are among the most useful insecticides commercially available. As Puerto Rico continues to have a prominent agricultural activity these compounds are still being used by a significant part of our population. Although only 14 cases of intoxication were identified over a 4 year period (3.5 per year), we need to stress the fact that this is a potentially lethal condition that requires prompt intervention for successful result.

Hayes et. al. collected 105 cases of organophosphates poisoning in Rhodesia and found that 42% were due to suicidal attempts, 10% to industrial or agricultural exposure and 36% to unknown etiology.<sup>6</sup> In the United States, Haddad found that suicide was also the most common mode of exposure followed by agricultural and industrial poisoning.<sup>7</sup> In our series 57% of the cases were



due to suicidal attempts and the remainder were due to accidental exposure. A psychiatric disorder was well established in 7 of the 8 patients with suicidal intention.

The finding that muscarinic signs and symptoms were more frequently present than nicotinic or central manifestation has been also reported by Whorton and Hayes.<sup>6, 8</sup> It has been reported however that nicotinic, muscarinic or central manifestations may occur in various combinations and may be present at different intervals after exposure in individual patients.<sup>2</sup>

The diagnosis of organophosphate poisoning is based on a history of exposure or contact, the presence of characteristic signs and symptoms and reversal of those symptoms with atropine and pralidoxime. The definite diagnosis of intoxication can only be made by direct measurement of acetylcholinesterase activity in the blood.<sup>4</sup> Direct measurement of organophosphates in the urine is done exclusively for research purposes.<sup>2</sup> At HURRA we do not have the facilities to measure this enzyme and it would probably not be cost effective in view of the few cases we have per year.

The most frequent cause of death in organophosphate intoxication is respiratory failure.<sup>4</sup> There are a number of basic measures that need to be instituted in the management of organophosphate intoxication. A patient with hypoxemia who is given Atropine has the risk of developing ventricular fibrillation, so it is vital to improve tissue oxygenation prior to atropine therapy. In our study 3 patients showed a Pa O<sub>2</sub> of less than 60 mm Hg while breathing room air.

Serum potassium (K<sup>+</sup>) should also be followed closely. Four of 14 patients (29%) had K<sup>+</sup> levels below 3.5 meq/liter. We also found that 5/14 patients (36%) had hyperglycemia (serum glucose >120) and that 10/14 or 71% had leukocytosis (WBC count >10,000). These three abnormalities have been reported previously and are all believed to be caused by increased release of catecholamines from the adrenal medulla.<sup>5</sup>

There are other laboratory abnormalities which have been reported in organophosphate poisoning. These include: glycosuria, proteinuria and hyperamylasemia.<sup>4</sup> These parameters were not measured consistently in our patients.

None of our patients developed seizures or ventricular arrhythmias. This complication had been reported to occur in less than 5% of cases by Hayes et. al.<sup>6</sup> We did have a patient who required mechanical ventilation for respiratory failure (Patient no.3) While being treated with atropine and pralidoxime, the signs and symptoms of toxicity reversed and he extubated himself, having no complications from the ventilator. Part of the clinical picture of organophosphate intoxication is bronchoconstriction, increased bronchial secretions and altered consciousness. Therefore the risk of developing pneumonia is quite high. We had 2 patients who developed clinical and radiographic evidence of pneumonic processes requiring intravenous antibiotics. Both patients were reported to have had an altered mental status (confusion and restlessness) and only one had increased bronchial secretions (Table 2).

Due to the lipophilic nature of organophosphates they may accumulate in the body and some patients may have

recurrence of the signs and symptoms of toxicity.<sup>2</sup> In the follow-up interviews none of the 10 patients reported any recurrence of symptoms.

Another important delayed toxicity of organophosphates is peripheral neuropathy. This manifestation was first described by Smith et al in 1930 and usually occurs 10 to 14 days after contact with the compound.<sup>9</sup> They tend to follow a protracted course with lifelong paresis.<sup>10</sup> Recovery is very unlikely and estimated to be less than 2%.<sup>11</sup> The compounds associated with neuropathy include DEF (DE Green), Merphos (Folex), and fenthion (Baytex).<sup>12</sup> None of these compounds were ingested by any of our patients. This finding compares favorably with the study of Hayes et al.<sup>6</sup> in which he reported only one case of neuropathy in a group of 105 patients.

It is believed that organophosphates can also phosphorylate an enzyme present in the myelin sheath. This enzyme has been called neuropathy target esterase (NTE) and has been found to be a marker of delayed neuropathy in animals.<sup>13</sup> There is a similar enzyme in peripheral blood WBC's and platelets.

Organophosphate poisoning is a potentially lethal situation. The use of appropriate supportive measures and the prompt institution of antidotal therapy are essential in order to achieve a good outcome.

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# CASE REPORT

## Cocaine and Rhabdomyolysis: Report of a Case and Review of the Literature

José Flaqué-Coma, MD

**Abstract:** Cocaine abuse is associated with a constellation of serious medical complications. An unrecognized and recently described complication of cocaine use is rhabdomyolysis with acute renal failure. We describe the first patient identified in our institution with this entity, admitted to the medical services with oliguric acute renal failure. Three days prior to admission the patient had a cocaine snorting binge. He presented with bilateral flank pain, gross hematuria, vomiting and chills. No history of crush injury, prolonged immobilization and or seizures was reported. On admission the vital signs were normal, physical exam revealed periorbital edema and marked soft tissue neck swelling. Lab values: Bun 120 mgs%, Creat. 10.7 mgs%, Na 132 meq/Lt, Co2 13mq/Lt, Cl, 103meq/Lt, Co2 13meq/Lt, Ca 5.3 mgs%, CPK 30,800 U/L with a MM fraction of 98%, LDH 600 U/L, SGOT 300 U/L. The urine was dark red with a ph of 6.5 and 100 rbc/hpf. The anti-GBM antibody and blood cultures were negative. An abdominal sonogram was normal. He received peritoneal dialysis and was discharged on his 14th hospital day with a CPK of 2,800 U/L and decreasing azotemia.

Cocaine associated rhabdomyolysis has only been recently described in the literature (AJM April, 88). Acute myoglobinuric renal failure needs to be added to the growing list of medical complications of cocaine use.

**Key words:** rhabdomyolysis, cocaine use, renal failure.

**A** growing literature is concerned with the severe complications associated with the abuse of cocaine.

An unrecognized and recently described complication of cocaine abuse is rhabdomyolysis with acute renal failure.

We describe the first patient identified with this complication in our institution and review the literature that supports the association of rhabdomyolysis with cocaine abuse.

### Case Report

A 25 y/o male was admitted to the medical service with a chief complaint of acute bilateral flank pain, gross hematuria, fever, chills and decreased urine output.

Three days prior to admission he had a cocaine snorting binge. No history of trauma, muscle compression, ethanol ingestion, seizures or prolonged immobilization was reported.

On admission no hypertension or hyperthermia was recorded. The physical exam revealed bilateral periorbital edema and soft tissue swelling of the neck. Laboratory data: BUN -120 mgs%, serum creatinine - 10.7 mgs%, serum Na - 132 MEQ/LT, Serum Cl-103 M/L - 16, Serum Ca - 5.3 mgs%, inorganic serum phosphorus - 7.0 mgs% Serum uric acid - 12 mgs%, LDH - than 600 IU/L, SGOT - than 300 IU/L, CPK - 30,800 IU/L with a MM fraction of 98%, Hgb -10 gms%, Hct-27.2%, platelet count 120,000/ul. The urine was dark red with a PH of 6.5, 100 rbc/Hpf and qualitative proteinuria. Blood cultures were negative and the antiglomerular basement membrane antibody and streptozyme test were reported negative. An abdominal sonogram was reported as normal.

The clinical course was characterized by oliguria and a rise in the azotemic parameters with a peak blood urea nitrogen of 134 mgs% and serum creatinine of 17.4 mgs%. The patient received acute peritoneal dialysis and on the eleventh day there was a brisk diuresis with eventual recovery of kidney function.

### Discussion

Non traumatic rhabdomyolysis has been reported in association with the illicit use of heroin,<sup>1</sup> amphetamines,<sup>2</sup> and marijuana.<sup>3</sup> Myoglobinuric acute renal failure is a common complication of rhabdomyolysis and follows both traumatic and non traumatic muscle injury.<sup>4</sup> More recently rhabdomyolysis has been associated with the use of cocaine.

A review of the literature yielded 63 patients with rhabdomyolysis associated to cocaine use. All reports were published after 1987.<sup>5-13</sup> In table I a summary is presented of the individual reports and the number of patients developing acute renal failure in each paper. Of the 63 pts. in this review 29 (46%) developed acute renal failure.

In table II a summary is presented of the clinical features of patients who developed acute renal failure as compared to those with cocaine related rhabdomyolysis who did not. In the majority of patients the route of cocaine ingestion was unknown. Severe liver dysfunction was seen in 16 of 23 (70%) of patients with renal failure as

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**Table 1 - Summary of Published Reports Describing Cocaine Associated Rhabdomyolysis**

Report of Cocaine Associated Rhabdomyolysis		
Author, Ref., Year	No. Pts.	Acute Renal Failure
Merigian ( 5) 87	1	1
Schwartz ( 6) 87	1	1
Barrido ( 7) 88	2	2
Krohn ( 8) 88	1	0
Herzlich ( 9) 88	3	3
Roth (10) 88	39	13
Faulkner (11) 89	5	5
Pogue (12) 89	4	4
Rubin (13) 89	7	0
Total	63	29 (46%)

**Table 2 - Characteristics of Patients with Cocaine Associated Rhabdomyolysis with and Without Renal Failure**

Characteristic	Renal Failure		(No. Pts.)
	Without	With	
IV Cocaine	13	10	
Smoked Cocaine	6	6	
Both	0	1	
Unknown Route	15	12	
Liver Dysfunction	2	16	
DIC	0	7	
Recovered Renal Function	-	17	
Died	0	6 (All Had DIC)	
DIC	-	-	
Oliguria	-	10	
Dialysis	-	14	

compared to 2 of 40(5%) who did not develop this complications.

Of the 63 patients in this review, 6 eventually died for a overall mortality rate of 9%. It is of interest that disseminated intravascular coagulation was reported in 7 patients, six of which eventually died. An oliguric phase was seen in 10 of the patients with acute renal failure and 14 of the 23 patients required dialytic support.

The largest series was reported by Roth et al in 1988.<sup>10</sup> This paper identified retrospectively 39 patients seen over an eight year period at a university hospital. Thirteen of the 39 patients (33 percent) had acute renal failure. The entire group of patients who died originated from this paper. In addition DIC as a complication of this entity was only reported in this paper.

In comparison to the patients with normal renal function, those with acute renal failure were more often admitted with hypotension (46 vs 4 percent), hyperpyrexia and markedly elevated serum creatinine kinase levels. Renal failure appears to have developed in the patients with more severe rhabdomyolysis.

The mechanism of cocaine associated rhabdomyolysis is unknown. There are several pharmacologic effects of the drug which may partially explain possible mechanisms. Cocaine blocks the pre-synaptic reuptake of norepinephrine and dopamine with a resultant increased sympathetic activity. This may cause arterial vasoconstriction and skeletal muscle ischemia leading to muscle injury. The sudden presentation of cocaine to skeletal muscle and the attendant arterial vasoconstriction may induce

rhabdomyolysis by tissue ischemia.

Hepatic dysfunction is often seen in patients with rhabdomyolysis. In a report of 119 patients with rhabdomyolysis of diverse etiologies, reversible hepatic dysfunction was seen in 30 patients (25%).<sup>14</sup> The pathogenesis of this finding is likely multifactorial and include hyperpyrexia, hypotension and release of proteases from injured muscle. In addition, there is some evidence implicating cocaine as a potent hepatotoxin in mice<sup>15</sup> and humans.<sup>16</sup>

Rhabdomyolysis can precipitate intravascular coagulation by the release of tissue thromboplastin and other activators of the coagulation cascade. The presence of intravascular coagulation appears to portend a grave prognosis with six of seven patients with this problem eventually dying.

This case report identifies acute rhabdomyolysis as an entity that needs to be added to the growing lists of complications associated with cocaine intoxication. The morbidity and mortality that accompany cocaine associated rhabdomyolysis warrant the attention of physicians.

#### Acknowledgment

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# ARTICULO ESPECIAL

## Satisfacción de los Pacientes con el Servicio de Salud en Tres Centros de Salud Familiar de la Región Noreste

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**Resumen:** La satisfacción con los servicios de salud depende en gran medida de la calidad de los servicios que se ofrecen y el trato personal que recibe el paciente del médico. En este estudio los parámetros utilizados para medir satisfacción con los servicios fueron: satisfacción con el trato y el manejo del médico, con los servicios de laboratorio, farmacia, radiología y de sala de emergencia. Se utilizó un cuestionario para recopilar la información de 319 pacientes en tres Centros de Salud Familiar de la Región Noreste. Los resultados indican que la mayoría de los pacientes están satisfechos con los servicios de laboratorio y de radiología pero no así con los de farmacia y los de sala de emergencia. Más de un 70% de los encuestados se sienten satisfechos con los servicios médicos recibidos. Las variables de edad y estado de salud fueron las únicas variables que correlacionaron con satisfacción de los servicios.

El Departamento de Medicina de Familia y Salud Comunal de la Escuela de Medicina de la Universidad Central del Caribe ha establecido talleres clínicos en los Centros de Salud Familiar de la Región Noreste en estrecha colaboración con el Departamento de Salud del Estado Libre Asociado de Puerto Rico. Esta relación ha permitido la descentralización del proceso docente hacia el cuidado primario y un adecuado balance entre la educación, la investigación y los servicios de salud.

La satisfacción que tienen los pacientes con los servicios de salud es un aspecto que ha sido utilizado para evaluar dichos servicios. Varios estudios han demostrado que ciertos patrones de conducta relacionados a la salud, como la habilidad de cumplir o seguir las instrucciones del médico, pueden ser afectados o influenciados por el grado de satisfacción que el paciente tenga con el servicio que se le brinda.<sup>1-11</sup> Es por ello que garantizar servicios de salud de excelencia es de vital importancia. Es necesario identificar aquellas áreas donde el paciente no se siente

satisfecho para poder hacer los ajustes necesarios que mejoran la calidad de los servicios. Durante la última década varios investigadores se han dado a la tarea de construir y definir sistemáticamente medidas válidas de satisfacción de los pacientes.<sup>1, 2, 9, 12</sup>

La literatura identifica varios indicadores que se relacionan altamente con la satisfacción que puedan tener los pacientes con los servicios de salud. Estos parámetros han sido consistentemente identificados en la literatura, y se pueden clasificar en cuatro áreas principales:<sup>1</sup> características del proveedor (rasgos de personalidad y calidad del servicio); (2) características de los pacientes (sociodemográficas, estado de salud); (3) aspectos de la relación médico-paciente (comunicación); (4) factores de estructura y manejo (accesibilidad del servicio, tiempo de espera, tratamiento, modo de pago).

Weiss<sup>1</sup> afirma que los indicadores que tienen que ver directamente con el médico y con el servicio (la interacción personal establecida entre el médico y el paciente, la accesibilidad al médico, contar con un médico de cabecera que atienda al paciente regularmente, tener un cuidado individualizado, recibir continuidad en el tratamiento, recibir atención a sus problemas personales y tener confianza en el sistema de salud); sobrepasan en importancia a los factores personales del paciente.

Aunque se ha correlacionado el grado de satisfacción del paciente con algunas de sus características sociodemográficas tales como edad, sexo, educación y nivel socioeconómico no se ha presentado un cuadro consistente sobre esta relación. Hay estudios que han reportado que los pacientes mayores expresan mayor satisfacción con el cuidado médico recibido.<sup>1, 3, 11, 13</sup> DiMatteo & Hays<sup>11</sup> especularon que los pacientes mayores simplemente pueden ver al médico más favorablemente o que el médico puede sentir un mayor sentido de urgencia al tratar a estos pacientes, por lo cual les provee mejor cuidado médico. Por otro lado, Ware et.al.<sup>12</sup> y Pope<sup>4</sup> no encontraron relación entre la edad y la satisfacción por los servicios de salud.

La condición de salud de las personas también se ha relacionado a la satisfacción con el cuidado médico recibido; generalmente cuando las personas están inca-



pacitados por los síntomas de una enfermedad demandan más de los servicios y se sienten menos satisfechos con los mismos.<sup>15, 16, 17</sup> También se ha encontrado que personas que se sienten felices con sus vidas tienden a estar más satisfechos con los servicios médicos recibidos.<sup>1</sup>

La relación entre el sexo del paciente y la satisfacción por los servicios ha sido estudiada por varios investigadores; hasta ahora los resultados han sido contradictorios. Algunos estudios han identificado que la mujer se siente un poco más satisfecha que el hombre con los servicios médicos recibidos y con el médico.<sup>11, 12, 18</sup> Mientras que otros no han encontrado ninguna relación entre estas dos variables.<sup>3, 13</sup> Por otro lado algunos estudios han reportado que existe un mayor grado de satisfacción con los servicios de salud entre los pacientes de clase social baja,<sup>14, 15</sup> mientras otros estudios han reportado que los ingresos y la satisfacción no están relacionados.<sup>11</sup>

Por lo antes descrito podemos concluir que los resultados de los estudios realizados hasta el momento con respecto a las características demográficas no son consistentes. Esto puede deberse a que los estudios han variado grandemente en el diseño, características de las muestras y las escalas utilizadas para medir satisfacción. Podemos entonces concluir que cada centro de cuidado médico tiene su peculiaridad, por lo tanto es de suma importancia conocer las características y necesidades de los pacientes que allí asisten para poder mejorar los servicios que se les ofrece.

Teniendo esta preocupación en mente se diseñó este estudio con el propósito de describir la satisfacción que tienen los usuarios de tres Centros de Salud localizados en la Región Noreste. Se estudiaron aquellos factores que influyen y afectan la satisfacción de los servicios de salud.

La hipótesis de este estudio es que la mayoría de los pacientes del Centro de Salud, están satisfechos con el servicio médico y con los servicios que paralelamente se les brinda, y que factores como edad, baja escolaridad y un buen estado de salud se asocian con altos niveles de satisfacción del paciente.

### Diseño y Metodología

Para este estudio descriptivo se entrevistaron todos los pacientes mayores de 18 años que acudieron a recibir servicios a tres Centros de Salud Familiar durante una semana del mes de febrero de 1990. Se utilizó un cuestionario para recopilar la información que fue entregado a los pacientes para que lo cumplimentaran, mientras se encontraban en la sala de espera.

Los indicadores utilizados para medir la satisfacción de los pacientes con los servicios brindados en el centro de salud fueron los siguientes: satisfacción con los servicios ofrecidos por el médico, radiología, farmacia, laboratorio, sala de emergencia y accesibilidad a los servicios médicos y de farmacia. Los factores que se correlacionaron con satisfacción de los pacientes fueron edad, sexo, plan médico, tener alguna condición crónica, escolaridad y calidad de servicio. Para el análisis estadístico de los datos se utilizó el programa estadístico SPSSPC.

### Resultados

Se entrevistaron un total de 319 pacientes de lo cuales 234 (75.5%) eran del sexo femenino y 76 (24.5%) del sexo masculino. La mayoría de éstos (62.6%) tenían 40 años o menos, un 10.0% de los pacientes eran de 65 años o más. El 72.1% recibía sus servicios a través de asistencia médica y "medicare". En cuanto al nivel de escolaridad de los pacientes se encontró que el 39.3% completaron entre 10 y 12 años de escuela (ver Tabla I). Al indagar sobre la accesibilidad al centro se encontró que el 55% de los pacientes indicaron que siempre se les hace fácil llegar al centro. De los 143 (45%) que indicaron hacerse difícil llegar al centro, el 23% (73) utilizaban la transportación pública.

Tabla I - Distribución de las Características Demográficas de los Encuestados

Características	N	Porcentaje
Sexo		
Masculino	76	24.5
Femenino	234	75.5
Edad		
18-30	115	36.7
31-40	81	25.0
41-50	47	15.0
51-64	38	12.1
más de 65	32	10.2
Años escolaridad		
0-6	65	21.3
7-9	65	21.3
10-12	120	39.3
más de 12	50	16.4

El 55.4% de los encuestados consideraban que tenían buena salud, considerando su edad. Un 36.7% de la muestra tenía al menos una condición de salud crónica (diabetes, hipertensión, artritis o enfermedad del corazón).

La Tabla II presenta el grado de satisfacción que tienen los pacientes con los servicios ofrecidos en los Centros de Salud Familiar. Un poco más de la mitad (56%) de los 196 pacientes que han utilizado sala de emergencia dijeron estar satisfechos o muy satisfechos con estos. La mayoría de los pacientes indicaron estar satisfechos con los servicios de laboratorio (80%) y de radiología (74%).

Tabla II - Distribución del Grado de Satisfacción que tienen los Pacientes con los Servicios Ofrecidos en los Centros de Salud Familiar

Servicio	Muy Satisfecho	Satisfecho	No Satisfecho	N
Médicos	49.0%	46.0%	5.0%	313
Sala de Emergencia	20.4%	35.6%	44.0%	196
Laboratorio	28.7%	51.4%	19.9%	222
Radiología	38.1%	36.4%	25.2	311
Farmacia	16.5%	44.9%	38.6%	303
Facilidades Físicas	13.7%	34.4%	51.9%	314

Para conocer el grado de satisfacción de los pacientes con los servicios de farmacia se utilizaron varios indicadores. En cuanto a la disponibilidad de los medicamentos en la farmacia el 80% de los pacientes reportó que los medicamentos están disponibles a veces; el 72% informó tener que esperar media hora o menos para que su receta sea despachada; y el 47% acude a una farmacia privada cuando los medicamentos prescritos no están disponibles en el Centro.

Se examinaron varios aspectos asociados a la relación médico-paciente que podrían afectar la satisfacción de estos últimos. El 70% de los encuestados entendía que el médico le explicaba claramente sobre el uso de los medicamentos prescritos, resultados de laboratorio y la condición de salud. El 89% (283) considera que el tiempo que el médico invierte en sus pacientes es adecuado. Igualmente una alta proporción de los pacientes (91%) indicó tener confianza en los conocimientos y habilidades del médico; y que éste les mostraba interés y entendimiento acerca de sus problemas de salud. Un 85% (263) sentía que su médico los trata con cortesía y respeto.

La mayoría de los encuestados (86%) indicó que prefiere verse siempre con el mismo médico. De éstos, el 60% manifestó que se les hacía difícil o un poco difícil ver al mismo médico siempre. Al preguntársele a los pacientes acerca del tiempo de espera para ver al médico, un 16% informó que usualmente espera media hora o menos; 33% espera una hora; 17% reportó esperar dos horas, y 34% indicó tres horas.

Se realizó un análisis de correlación para determinar si existía asociación entre la medida de satisfacción general con los servicios y la edad, el sexo, la escolaridad y el tener una enfermedad crónica (ver Tabla III). Se encontró una asociación negativa entre la satisfacción con los servicios y la edad del paciente (a menor edad mayor satisfacción,  $r = -.21$ ,  $p < .01$ ) y el grado de escolaridad ( $r = -.01$ ). No se pudo establecer ninguna asociación entre el sexo, tener una enfermedad crónica o tener plan médico y la satisfacción con el servicio.

deran deben mejorarse. Estos consideraban que todos los servicios deberían de ser mejorados en especial los de farmacia (66%), sala de emergencia (51%), citas médicas (43%) y trato al paciente (36%).

### Discusión y Conclusión

Estudios en el área de satisfacción de los pacientes con los servicios han demostrado que este componente garantiza la continuidad de su cuidado. Al reconocer la satisfacción del paciente como una influencia en su conducta con relación a su salud, no es sorprendente ver el aumento de esfuerzo que existe para entender mejor al paciente como un ente consumidor del servicio. La planificación de los servicios y programas educativos deben tener en cuenta las características de la población que se atiende.

La población de este estudio se podría describir como una mayormente femenina (76%), relativamente joven (62.6% menor de 40 años) y con una escolaridad no mayor de 12 años de estudio (83.6%). El hecho de que un 45% de los pacientes indique que se les hace difícil llegar al centro es algo que se debe tener en consideración para mejorar el sistema de citas y periodo de espera para recibir los servicios del médico, de la farmacia, del laboratorio y de radiología.

Los encuestados indicaron tener menos satisfacción con los servicios de emergencia, radiología y farmacia. Estas mismas áreas son las que se señalan deben mejorarse. El que un 47% de los pacientes tenga que comprar los medicamentos recetados siendo médico indigente nos lleva a pensar en la necesidad de establecer una estrecha coordinación entre los médicos (tipo de medicamento que prescriben) y farmacia (medicamentos disponibles).

Se encontró que existen unas comunidades mayormente satisfechas con el servicio que reciben en sus Centros de Salud Familiar pero aun necesitan mejorar algunas áreas. A pesar de que aproximadamente 90% de los encuestados indicó tener confianza en los conocimientos y habilidades del médico y el tiempo que invierte el médico en los pacientes, un 30% no recibe explicación clara sobre su condición de salud, medicinas y laboratorios, y un 15% no sentía que el médico les trataba con respeto y cortesía.

La continuidad en la atención médica ha sido uno de los factores que ha sido identificado en la literatura como indicador de un buen mantenimiento de salud y de altos niveles de satisfacción en las poblaciones estudiadas. Un 60% de los encuestados manifestó no poder lograr verse con el mismo médico.

La óptima calidad de los servicios de salud es la meta común de los proveedores de cuidado médico. La satisfacción del paciente es un indicador importante de garantía de calidad y excelencia en el servicio. Los cambios ocurridos durante la pasada década en el sector salud recalcan la importancia del consentimiento y la participación ciudadana en la salud individual y colectiva. El estudio que presentamos es parte de nuestros esfuerzos por integrar la docencia con los servicios primarios de salud de la Región Noreste, y que esta relación redunde en el mejoramiento de la calidad del cuidado médico que recibe el paciente.

**Tabla III - Coeficientes de Correlación entre la Satisfacción General con los Servicios y las Variables Sociodemográficas**

Parametros	r	N	Significancia
Sexo	.01	293	N.S.
Edad	-.21	289	.001
Escolaridad	.14	304	.01
Enfermedad			
Crónica	-.06	317	N.S.
Plan Médico	.03	289	N.S.

Por último se les preguntó a los pacientes si volverían al Centro de Salud a recibir servicios médicos. Un 42% (163) indicaron que volverían porque estaban satisfechos con el servicio mientras que el 53% (163) indicaron que volverían porque no tienen plan médico privado. Solo un 5% indicó que no volvería al centro a recibir servicios. También se les preguntó sobre las áreas que ellos consi-



### Reconocimiento

Queremos agradecer a los estudiantes de medicina de cuarto año de la clase de Salud Comunal II por su participación y realización de este estudio. Nuestro agradecimiento también se extiende a los directores médicos y al personal de los Centros de Salud Familiar por permitir que este estudio se realizara.

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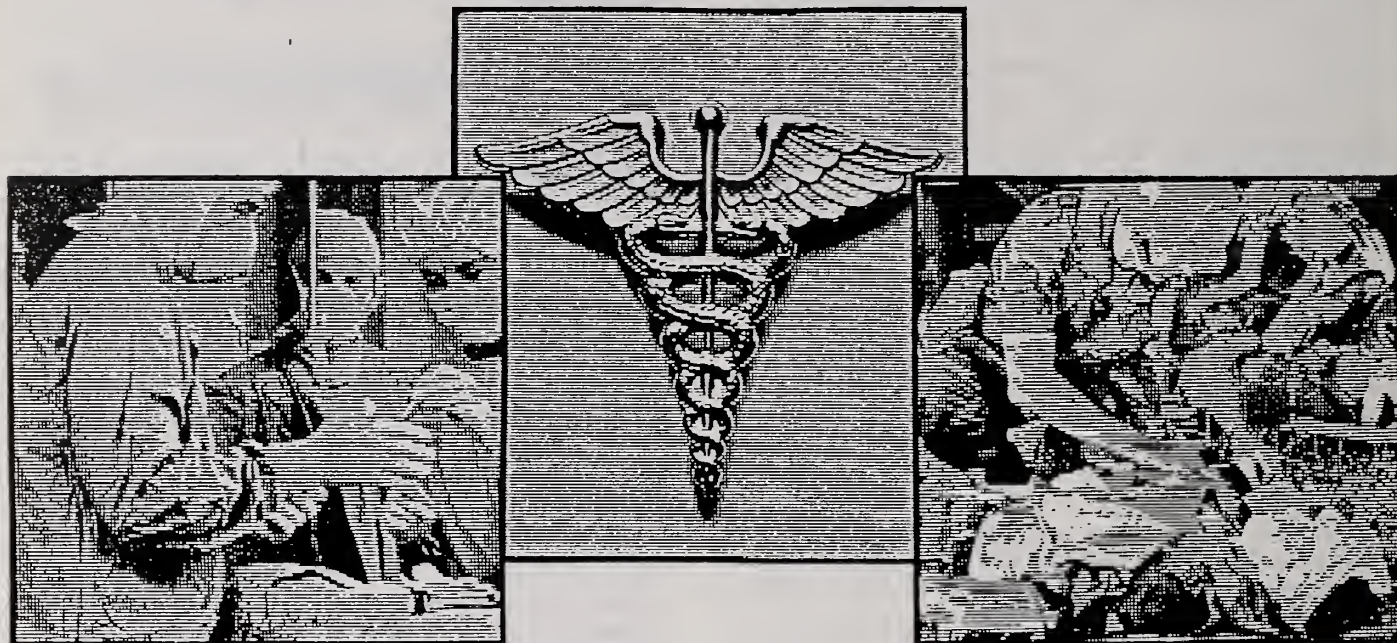
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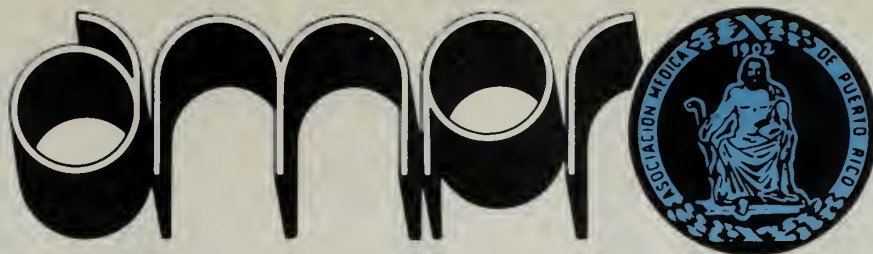
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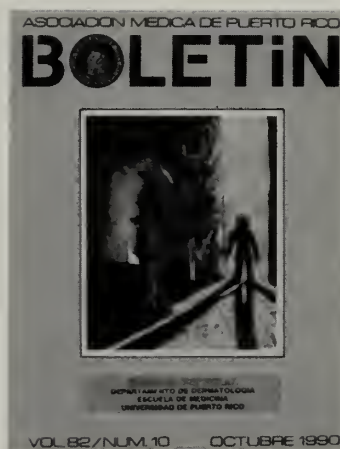
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Giampiero Rosati nació en Florencia, Italia, en el 1946. Estudió en el Liceo Artístico y en "L'Accademia di Belle Arti" de Florencia. Reside en San Juan, Puerto Rico.

Rosati ha participado en varias exposiciones colectivas y ha tenido una exposición individual en Florencia. Ha sido premiado en varias ocasiones.

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Actualmente es profesor de Arte en la Escuela de Artes Plásticas y en la Liga de Arte en San Juan. La Junta Editora del Boletín de la Asociación Médica de Puerto Rico agradecen al autor y a la Dra. Norma Cruz-Mendieta su valiosa colaboración con nuestra revista.



## La Importancia de la Investigación Clínica

**L**a curiosidad es la madre de la Filosofía. Solo al uno cuestionar los datos que la vida nos presenta puede uno crecer y desarrollarse.

Se dice que algunos de los descubrimientos más importantes han sido por casualidad e incluso en Inglés existe la palabra "Serendipity" para explicar este fenómeno. El término está basado en las hijas de Serendip en el Ceilán que así descubrían las cosas. Ejemplos de estos descubrimientos, por casualidad, son el de América, la Penicilina, el virus de la Hepatitis B y la tinción por el efecto del calor del Bacilo de Tuberculosis. Pero la casualidad solo puede ser aprovechada por aquel que ya está buscando respuestas a sus preguntas.

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Estas páginas están llenas de preguntas y respuestas. Aquellos que llevan a cabo esta investigación están desarrollándose a sí mismos como profesionales y compartiendo este conocimiento con sus compañeros para hacerlos crecer y hacer crecer su especialidad de Dermatología. Hacer investigación clínica es hacer buena medicina. Los profesionales de la Medicina tienen la obligación de enseñarles a sus estudiantes que esta es la manera cómo se crece intelectualmente en nuestra profesión.

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1. Data on file, G.D. Searle & Co.
2. 1988 Joint National Committee: The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1988;148:1023-1038.

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**Contraindications:** Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

**Warnings:** Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

**Precautions:** Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration.

Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

**Adverse Reactions:** Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°, 2°, 3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, increased urination, spotty menstruation, impotence.

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# DERMATOLOGY DIAGNOSIS

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**T**his is an 18-month-old female born to a G1 P1 A0 female after an uncomplicated delivery. Approximately one week after birth, the infant developed a diffuse bullous eruption. The mother denied fever, seizures, illness or use of medications in the patient or during her pregnancy. On evaluation the patient was found to have linearly arranged inflammatory vesicles and bullae involving the upper extremities, lower extremities, and trunk, but sparing the face. The rest of the physical examination was unremarkable. No developmental or neurologic abnormalities were appreciated at that time. A skin biopsy was done and a presumptive diagnosis made. The patient was followed regularly thereafter. A gradual change in the appearance of the lesions occurred. Family history was negative for similar skin lesions and other skin disease.

Present physical examination was remarkable for verrucous plaques and papules distributed in linear arrays along the lower extremities and trunk. There were also verrucous plaques at both axillae and four bullae with an erythematous base linearly arranged along the medial left calf. There were no mucosal lesions, and no abnormalities of the hair and nails. The rest of the physical and neurologic examinations was unremarkable.



## WHAT IS YOUR DIAGNOSIS?

- A. Systematized epidermal nevus
- B. Incontinentia pigmenti
- C. Allergic contact dermatitis
- D. Atopic dermatitis

### Diagnosis: Incontinentia Pigmenti

Incontinentia pigmenti (Bloch-Sulzberger syndrome) is a hereditary disorder with characteristic cutaneous findings and associated ocular, dental, skeletal, and central nervous system defects. The features of this disorder were first delineated by Bloch and Sulzberger in separate reports in 1926<sup>1</sup> and 1927,<sup>2</sup> respectively. In 1976, Carney<sup>3</sup> published a review of the world literature on incontinentia pigmenti providing an extensive statistical analysis of the epidemiologic, clinical, and histopathologic aspects of this disease.

Incontinentia pigmenti (I.P.) primarily affects females with a female to male ratio of approximately 37:1.<sup>3</sup> Although the genetics of this disease has not been completely elucidated, the pattern of inheritance is thought to be X-linked dominant with lethality in males.<sup>3, 4</sup> Living males, as well as affected females born to women without the disease, probably represent spontaneous mutations. Most cases of I.P. have occurred in caucasians, although the disease has also been reported in blacks, hispanics, and peoples of Asian descent.<sup>3</sup> Women with I.P. have an increased incidence of spontaneous abortions and miscarriages.

The cutaneous eruption that characterizes I.P. is classically described as having three distinct stages of evolution; some authors have added a fourth stage.<sup>3</sup> Overlap of these stages is common. The first stage usually begins within six weeks of birth (96% of patients) with the appearance of irregular, linearly arranged, inflammatory vesicles and bullae erratically distributed over the trunk and extremities; when more localized in distribution, the lesions are usually limited to the extremities. New crops of these lesions may continue to appear for up to several months. There have been rare reports of onset of these lesions in late infancy and adulthood.

The second stage or verrucous stage usually begins between the second and sixth week of life with similarly arranged verrucous or warty lesions on one or more extremities, most often localized on the dorsal aspect of the hands and feet. These lesions usually resolve within months, often leaving residual atrophy and/or pigmentation.

The third or pigmentary stage, the hallmark of the disease, begins at 12-16 weeks of age with the appearance of streaks, whorls, and splashes of tan, brown, or slate-gray pigmentation asymmetrically distributed over the trunk and extremities. This pigmentation does not necessarily follow the pattern, shape, or location of the first two stages. The pigmentation usually intensifies until the age of 2 years and gradually fades thereafter so that it is almost completely gone by young adulthood. Four to forty percent of the patients with I.P. will be born with the skin lesions of the third stage<sup>5</sup>—it is assumed that in these patients the first two stages occurred in utero.

The fourth stage of the cutaneous eruption consists of depigmented and atrophic patches and streaks on the torso and extremities. Recognition of these lesions is important as they may be the only remnants of I.P. in adults. However, the incidence, histologic findings, and pathogenesis of this stage are poorly defined. In his

survey, Carney found that this stage was reported in about 2/5 of patients with I.P.<sup>3</sup>—this probably underestimates the true incidence of these lesions as they may have gone unnoticed in many patients.

Other cutaneous changes in I.P. include hair and nail defects. Alopecia with or without scarring, usually of the vertex of the scalp, will be found in 37.8% of patients. Dystrophy of all or most nails of the fingers and toes has been reported in approximately 7% of patients, but the significance of its association with I.P. is not known as the prevalence of onychodystrophy in the general pediatric population is not known.

In addition to the characteristic cutaneous findings, 80% of patients with I.P. have one or more associated defects of the eyes, teeth, or central nervous system.<sup>3</sup> Dental defects occur in 68% of patients and include, in descending frequency, partial or complete anodontia, pegged or conical teeth, and delayed dentition.<sup>3, 6</sup> Ocular defects occur in 35% of patients and include nystagmus, cataracts, corneal opacities, retinal detachment, retinal damage by vascular proliferation and pigmentation, microphthalmus, optic nerve atrophy, and optic nerve gliomas. Blindness can occur in up to one fifth of the patients. Neurologic abnormalities include seizure disorders, mental retardation, microcephaly with associated cortical atrophy and/or hydrocephalus, spastic paralysis, and cerebellar ataxia. Skeletal and developmental abnormalities (13% of patients) include, in decreasing order of frequency, skull deformities, dwarfism, club foot, spina bifida, cleft palate and/or cleft lip, hemiatrophy, congenital dislocated hip, chondrodystrophy, and other anomalies such as supernumerary ribs or syndactyly. A few patients have had congenital hearing loss or congenital heart disease.

The diagnosis of I.P. is basically a clinical diagnosis—the bizarre pattern of the skin lesions is characteristic, especially in the third stage of the cutaneous eruption. Drug eruptions, pyodermas, and the various vesiculobullous diseases of infancy and childhood may be considered in the differential diagnosis of the first stage. Epidermal nevus is probably the main consideration during the second stage. A skin biopsy may be helpful in confirming the diagnosis and ruling out other disorders, but the histologic findings, which vary with the stage of the disease, are not diagnostic.

Laboratory investigations do not reveal any characteristic abnormality except that during the first stage of the cutaneous eruption three fourths of the patients will show a leukocytosis with an eosinophilia of 5-65% during the first two weeks of life; a mean eosinophilia of more than 5% will then persist until about the 20th week of life.<sup>3</sup>

There is no cure for this disease. Treatment is mainly symptomatic and supportive. Antibiotics should be given only if infection develops. Associated anomalies should be looked for. Affected individuals should receive regular ophthalmologic follow up given the potentially severe eye disease. It is not known, however, if prevention of the visual sequelae is possible. Probably, patient education and genetic counseling are the most important aspects in the management of these patients.



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# REVIEW ARTICLE

## Cutaneous Drug Reactions

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**Summary:** Cutaneous drug reactions are among the most common causes of skin eruptions in hospitalized patients. In outpatient clinics, drug eruptions represent a diagnostic and therapeutic challenge to the physician as any drug can cause an adverse cutaneous reaction. These reactions may be mediated by immunologic or non-immunologic mechanisms. Cutaneous drug reactions may manifest themselves in various clinical morphologic patterns. Factors such as sun-exposure, concomitant drugs or diseases and host immune status can influence the type and morphology of lesions.

History taking is one of the most important aspects in the evaluation of these patients and must be oriented so as to provide the information that will lead to the final diagnosis.

Cutaneous drug reactions are among the most frequent side effects of medications. Because the skin reacts to various stimuli with a limited number of reaction patterns, the recognition of a drug reaction may prove to be a diagnostic challenge. Not only do different drugs produce similar reaction patterns, but many cutaneous drug reactions mimic other skin diseases.

Cutaneous drug reactions may be classified with respect to their pathogenesis. In this regard, they may be divided into immunologic and nonimmunologic reactions. Immunologic reactions, also known as allergic drug reactions, are those mediated by immunologic mechanisms which include IgE-dependent, cytotoxic, immune complex-mediated, and cell-mediated mechanisms. Nonimmunologic reactions are those not mediated by the host's immune system and include side effects, toxicity, overdose, cumulation, tolerance, drug interactions, and others. Nonimmunologic reactions to drugs outnumber allergic drug reactions.<sup>1</sup>

Cutaneous drug reactions may also be classified with respect to the morphology of the skin lesions that they produce. These reaction patterns and their more commonly precipitating agents are listed in Table I.

TABLE I: CUTANEOUS DRUG REACTIONS CLASSIFIED ACCORDING TO MORPHOLOGIC PATTERN

Morbilloform	Acneiform	Penicillamine
Ampicillin	Androgens	Penicillin
Amoxicillin	Corticosteroids	Phenylbutazone
Penicillin	Cyclosporin	Practolol
Gentamicin	Dactinomycin	Procainamide
Sulfonamides	Haloperidol	Propylthiouracil
Griseofulvin	Hydantoins	Quinidine
Acetylsalicylic acid	INH	Reserpine
NSAIDS	Lithium	Streptomycin
Barbiturates	Methotrexate	Sulfonamides
Gold	Oral contraceptives	Tetracyclines
Hydantoins	Quinidine	Vesiculobullous (pemphigus-like)
Thiazides	Purpura	Captopril
Tetracyclines	Acetaminophen	Penicillamine
Urticaria/Angiodema	Allopurinol	Penicillin
Acetylsalicylic acid	Digoxin	Phenobarbital
NSAIDS	Furosemide	Piroxicam
Allopurinol	Gold salts	Rifampin
Aminoglycosides	Lidocaine	Vesiculobullous (pemphigoid)
Antimalarials	Methyldopa	Clonidine
Barbiturates	Penicillin	Furosemide
Blood products	Phenylbutazone	PCT-like
Gold	Quinine	Furosemide
Hydantoins	Quinidine	Nalidixic acid
Phenothiazines	Rifampin	Tetracyclines
Penicillin	Sulfonamides	Erythema multiforme
Saccharin	Cimetidine	Acetylsalicylic acid
Sulfonamides	Clorazepate	Amoxicillin
Thiamine	Dilantin	Ampicillin
Thiouracil	Disulfiram	Dapsone
Fixed drug eruption	Erythromycin	Penicillin
Penicillin	Hydralazine	Tetracyclines
Sulfonamides	Ketoconazole	Sulfonamides
Streptomycin	Levamisole	Dilantin
Tetracyclines	NSAIDS	Phenobarbital
Acetaminophen	Propylthiouracil	Gold salts
NSAIDS	Tetracyclines	Hydralazine
Antihistamines	Thiazides	Ketotifen
Digoxin	SLE-like syndrome	NSAIDS
Gold salts	Acetylprocainamide	Penolphthalein
Hydralazine	Aminosalicylic acid	Sulfonamide hypoglycemics
Phenothiazines	Allopurinol	Toxic epidermal necrolysis
Lichenoid	Captopril	Allopurinol
Antimalarials	Chlorthalidone	Cephalexin
Captopril	Chlorpromazine	Cephmandole
Chlorpropamide	Cimetidine	Penicillin
Demeclocycline	Clonidine	Rifampin
Furosemide	Dilantin	Sulfonamides
Gold	Griseofulvin	Tetracyclines
Levamisole	Hydralazine	Barbiturates
Penicillamine	INH	Carbamazepine
Phenothiazines	Lithium	Dilantin
Propanolol	Nitrofurantoin	NSAIDS
Thiazides	Oral contraceptives	Phenolphthalein

Maculopapular and urticarial reactions are the most common<sup>2</sup> and toxic epidermal necrolysis is probably the most serious.

A thorough review of the different cutaneous drug reactions is beyond the scope of this paper. It is our purpose to present an overview of the subject emphasizing the more common morphologic presentations of drug reactions and their etiologies. Cutaneous reactions to topically applied drugs have been excluded. The pathogenesis of the various reaction patterns is discussed in each section, when known.

### Maculopapular reactions

Morbilloform ("measles-like") eruptions are the most common of the drug-induced cutaneous reactions.<sup>2</sup> The



skin lesions consist of erythematous macules and papules that usually appear in a symmetric distribution over the trunk and extremities. As new lesions appear, they may coalesce to form patches of erythema. Similar lesions may also occur in the oral mucosa. A low grade fever is often associated with the eruption, as is moderate to severe pruritus.

The eruption usually begins about one week after onset of therapy with the offending agent, and usually lasts one to two weeks. However, with some drugs such as penicillin, onset of the eruption may occur up to two weeks after discontinuation of therapy.<sup>3</sup> Reactions due to gold may appear as late as 2 years after discontinuation of therapy.<sup>3</sup>

The mechanism by which these eruptions occur is unknown. Because morbilliform reactions clinically resemble the appearance of the acute graft versus host reaction, cytotoxic and cell-mediated immune mechanisms have been proposed.<sup>1</sup> However, the fact that these reactions do not always recur with repeated exposure cannot be explained by these mechanisms.

The main consideration in the differential diagnosis is viral exanthem. Routine laboratory studies are rarely helpful. The presence or absence of peripheral eosinophilia is of little value in excluding or confirming the diagnosis.<sup>3</sup> Histologic findings on skin biopsy may be helpful in supporting the diagnosis.

Morbilliform eruptions, as other drug eruptions, usually fade with withdrawal of the offending drug. As previously mentioned, occasionally the rash will fade despite continued use of the drug.

Drugs commonly causing these eruptions are listed in Table I. The morbilliform eruption seen in patients with mononucleosis taking ampicillin may also occur with amoxicillin.<sup>3</sup>

### **Urticaria/angioedema**

Urticaria is characterized by wheals of variable sizes that are usually mildly pruritic. These lesions merely represent edema and inflammation in the superficial layers of the skin, specifically, the papillary dermis. When the edema and inflammation involve the deep dermal and subcutaneous tissues, the cutaneous reaction is then referred to as angioedema. Angioedema involving the skin and/or mucosal surfaces may be part of a severe anaphylactic reaction.

Urticarial episodes may be classified as acute or chronic, the former referring to those episodes lasting less than six weeks and the latter referring to those episodes lasting more than six weeks. In contrast, the individual lesions of urticaria usually appear suddenly within minutes to days after exposure to the offending agent, and last less than 24-48 hours. The IgE-mediated urticarial reactions that will be discussed below are called immediate reactions if they occur within minutes to hours after drug exposure, and accelerated reactions if they occur between 12-36 hours after drug exposure.

Drugs may cause both acute and chronic urticaria and represent one of the many possible etiologies of this cutaneous reaction. The most frequently involved agents are aspirin, penicillin and blood products.<sup>1, 3</sup> However, almost any drug can cause this type of reaction. A list of

the more commonly involved agents appears in Table I.

The pathogenesis of urticaria and angioedema involves the release of chemical mediators from the granules of tissue mast cells and circulating basophils. These mediators include histamine, chemotactic factors, and metabolites of arachidonic acid. Degranulation of mast cells and basophils may be caused by immunologic and nonimmunologic mechanisms.<sup>4</sup> Immunologic activation of mast cells is mediated by IgE (type I hypersensitivity reaction). Urticarial eruptions caused by penicillin occur by this mechanism. Nonimmunologic activation of mast cell degranulation, as the name implies, is not mediated by IgE. Drugs such as opiates, polymyxin B, curare, D-tubocurarine and radiocontrast dyes have been shown to directly stimulate mast cell degranulation.<sup>1</sup> Other drugs may act through the alteration of arachidonic acid metabolism.<sup>3</sup> This appears to be the mechanism in aspirin and nonsteroidal anti-inflammatory agent-induced urticarial eruptions. Interestingly, sodium salicylate and choline salicylate, two drugs with a chemical structure similar to that of aspirin, do not cause mast cell degranulation.

Type III hypersensitivity reactions, that is, those mediated by deposition of circulating immune complexes, may also be a mechanism responsible for drug-induced urticaria. In these cases, immune complex deposition results in a clinical syndrome known as serum sickness characterized by an urticarial or papular eruption associated with fever, lymphadenopathy, myalgias, arthralgias, arthritis, nephritis and neuritis. In contrast to the other urticarial eruptions already discussed, serum sickness has a more prolonged incubation period. It usually occurs within one to three weeks of exposure to the offending drug. Serum, penicillins, and sulfonamides are the drugs which most often cause this type of cutaneous reaction. Other commonly involved drugs include acetylsalicylic acid, cephalosporins, dextrans, hydralazine, hydantoins, phenylbutazone, streptomycin, thiouracils, and radiocontrast dyes. More recently, minocycline and naproxen have also been reported to cause this reaction pattern.<sup>4</sup>

### **Fixed drug eruption**

Fixed drug eruption is a peculiar drug-induced dermatosis which is characterized by one or more circumscribed, dusky red, target-like lesions that always occur at the same sites upon repeated exposures to the offending drug. Lesions may vary in size from small macules to large plaques and usually appear suddenly after the ingestion of certain drugs. The induction period is frequently within the first three days after exposure to the drug. The mucosa of the mouth and genitalia may be involved, in which case, swelling, erythema and sometimes even blistering may occur.

Cutaneous lesions evolve from erythematous macules to edematous, dusky brown plaques that can progress to vesiculation. They finally resolve leaving a residual hyperpigmented patch (Figure 1). Characteristically this hyperpigmentation will become accentuated with each subsequent challenge. The face, trunk and genitalia are most frequently involved. Symptoms may vary from burning and pain in early lesions to itching in more



Figure 1. Hyperpigmented macules in fixed drug eruption.

established lesions. It is still unknown why lesions present this selective predilection for only certain sites, but it is thought that fixed drug eruptions are mediated by type IV immunologic tissue damage in which the drug acts as a hapten and antibody dependent cellular cytotoxicity follows.<sup>5</sup>

The histopathology shows vacuolization of the basal cell layer and a lymphohistiocytic infiltrate of the dermis which leads to pigmentary incontinence.

Substances frequently invoked as causative agents of this condition include those depicted in Table I.<sup>3</sup>

### Lichenoid drug eruptions

Lichenoid drug eruption describes an eruption in which the cutaneous lesions clinically resemble classical lichen planus (Figure 2). These lesions may occur in a widespread or localized distribution. Clinical findings on the skin of affected patients may also include other skin lesions, namely pigmentary changes or eczematous, hypertrophic, pityriasis rosea-like, and photodistributed lesions, among others. Violaceous discoloration of lichen planus-like lesions is the most common clinical finding that makes this drug-induced dermatosis so closely similar to true lichen planus, but Wickham's striae (whitish reticular lines) a distinguishing feature of lichen planus is not commonly seen in lichenoid eruptions.

Clinical manifestations are chiefly confined to the integumentary system including the mucous membranes. Many of the classical drugs associated with lichenoid eruptions may also cause other forms of systemic side effects which may coexist with this dermatosis (eg. gold salts, antimalarials, phenothiazine).

The pathogenesis of this type of drug eruption is thought to involve a type IV or cell-mediated tissue injury since microscopic examination of skin lesions shows both an inflammatory infiltrate mostly composed of helper T-



Figure 2. Lichenoid drug eruption.

cell lymphocytes and vacuolar degeneration of the basal layer as seen in many other antigen-mediated cytotoxicity disorders.<sup>7, 8</sup> The presence of tissue eosinophilia helps to differentiate this eruption from classical forms of lichen planus.<sup>3</sup>

The evolution of this pattern of drug eruption may be insidious or abrupt depending on the particular drug, but requires either a previous or a cumulative exposure to the substance in order for the eruption to be expressed.

Lichenoid dermatitis is seen most frequently after exposure to drugs through oral intake. Contact exposure is known to be responsible in at least two instances, namely mercury in dental amalgam, with lichen planus-like stomatitis and paraphenylenediamine in film color developer in which a late intense lichenoid and eczematous eruption on the exposed areas of the hands and arms is seen. Agents implicated in this type of drug eruption are listed in Table I.

### Acneiform eruptions

Acneiform eruptions are characterized by lesions which resemble acne vulgaris and which consist mainly of papules and pustules with the absence of comedones. The lesions characteristically tend to have a sudden onset, tend to occur in adult patients, and tend not to be confined to the usual sites of acne vulgaris.<sup>9</sup>

Steroid folliculitis is one of the best known acneiform eruptions (Figure 3). It may occur as early as two weeks after starting corticotropin (ACTH) or corticosteroids.<sup>10</sup>





Figure 3. Steroid-induced acne.

The lesions are usually all in the same stage of development and affect mainly the trunk and upper arms with relative sparing of the face.<sup>10</sup> Prolonged application of steroids to the skin, especially if under occlusion, may also cause a folliculitis.

Other drugs which may cause an acneiform eruption are shown in Table I. Among these, halogen acne must be considered in patients using sedatives, expectorants and vitamins with mineral supplements that contain bromides or iodides. Among the chemotherapeutic agents, dactinomycin is known to cause an acneiform eruption.<sup>11</sup>

Chloracne is an occupational disease due to exposure to chlorinated hydrocarbons. The lesions are very inflammatory and consist of papules, pustules, nodules, large comedones, and cysts most commonly on covered areas.<sup>10</sup> Contact with insoluble cutting oils and coal tar derivatives may produce a similar picture.

### Drug-induced purpuras

Purpuras induced by medications may be classified into those secondary to thrombocytopenia, those induced by vasculitis and the anticoagulant necroses. Some drugs induce the formation of antiplatelet antibodies causing a thrombocytopenia which may lead to nonpalpable purpuras. Drugs which may induce the formation of antiplatelet antibodies are shown in Table I.<sup>9</sup>

Drugs may be a factor in the precipitation of necrotizing vasculitis. The mechanism involved in this event is believed to be that of deposition of immune complexes within vessel walls with the subsequent activation of the complement cascade.<sup>12</sup>

The anticoagulant necroses include Coumadin and heparin necrosis. Coumadin necrosis (warfarin necrosis) is a rare complication of Coumadin anticoagulant therapy and is seen in 0.001% - 0.7% of those started on the medication.<sup>13</sup> Typically, lesions appear between the third and tenth day of treatment and consist of well-defined painful purpuric patches that progress to hemorrhagic bullae and necrotic lesions.<sup>14</sup> Most patients are women, usually obese and middle-aged, and the areas most commonly affected are those with abundant subcutaneous fat such as the breasts, buttocks, abdomen, and thighs although cases involving other parts of the extremities and the penis have been reported.<sup>15</sup> Histopathology of the skin lesions shows occlusion of dermal and

subcutaneous vessels with fibrin thrombi without signs of inflammation.<sup>16</sup>

A heterozygous protein C deficiency state is believed to be an important predisposing factor for the development of Coumadin necrosis.<sup>13</sup> Protein C is a vitamin K-dependent potent anticoagulant factor in plasma. It has a shorter half-life than most vitamin K-dependent clotting factors (factor II, IX and X) so that after the start of warfarin, there is a transient hypercoagulable state where protein C has been depleted but these clotting factors have not.<sup>13</sup>

The treatment of Coumadin necrosis consists of discontinuing the medication and administering vitamin K and high dose intravenous heparin.<sup>17</sup> The areas affected heal with extensive scarring and in some cases skin grafting or amputation may be necessary.<sup>14</sup>

Heparin necrosis presents with a clinical and histologic picture similar to Coumadin necrosis.<sup>18</sup> It usually occurs 6 to 13 days after the onset of treatment and is associated with the development of thrombocytopenia for which reason an immunologic mechanism has been proposed.<sup>18</sup> It occurs mostly at sites of subcutaneous injections of heparin although it has been reported at distant sites during intravenous heparin administration with no specific site of predilection.<sup>18</sup> The mechanism involved is that of intravascular thrombosis induced by a heparin-dependent aggregating factor which is believed to be an immunoglobulin.<sup>18</sup> Treatment consists of termination of heparin therapy and administration of oral anticoagulation.<sup>18</sup>

In the differential diagnosis of anticoagulant necrosis, thrombosis induced by the use of intravenous cocaine must be considered.<sup>19</sup> In a recent case report, the lesions began to appear within minutes of an overdose with intravenous cocaine and showed a similar progression to that of anticoagulant necrosis.

Alteplase (tissue plasminogen activator) is a recently developed recombinant fibrinolytic increasingly used in the treatment of acute myocardial infarction (MI). A case report of painful purpuras at sites of prior cutaneous trauma following treatment with this thrombolytic in a patient with acute MI has appeared recently in the literature.<sup>20</sup> Histopathology of a skin biopsy failed to show evidence of leukocytoclastic vasculitis or fibrin thrombi.

### Drug-induced systemic lupus erythematosus-like syndrome

Drug-induced systemic lupus erythematosus (SLE)-like syndrome, also known as drug lupus or hydralazine lupus syndrome,<sup>9</sup> represents a relatively benign form of lupus induced by certain drugs which is characterized by the presence of antinuclear antibodies (ANA) along with the presence or absence of the signs and symptoms closely associated with SLE. The drugs most commonly involved<sup>16</sup> in producing this clinical picture are procainamide (antiarrhythmic), hydralazine (antihypertensive), and dilantin (anticonvulsant) but a long list of drugs have been associated with this condition (see Table I). It is believed that this syndrome is drug-induced but some drugs such as penicillamine are believed to act through unmasking a latent SLE.<sup>9, 16, 21</sup> The pathogenesis of these reactions is still uncertain: both immunologic (type II

through IV) and pharmacologic mechanisms have been suggested.<sup>22</sup> Drug-induced SLE-like syndrome tends to affect older people and more men when compared with SLE.<sup>23</sup>

After starting the treatment with the offending drugs patients can present with malaise, fever, arthralgias and pleuritic pain. Others can also develop adenopathy and hepatosplenomegaly.<sup>24</sup> Cutaneous lesions can present in up to eighteen percent of the cases, including erythema on sun exposed areas, erythema nodosum, pruritic papular skin lesions, purpura and lesions typical of SLE.<sup>21</sup> Pyoderma gangrenosum-like ulcers were reported in a patient with SLE-like syndrome.<sup>21</sup> Hydrochlorothiazide has been reported to cause subacute cutaneous lupus erythematosus.<sup>25</sup> Different from SLE, drug-induced SLE-like syndrome shows a lower incidence of skin, renal and CNS abnormalities but pleuropulmonary manifestations are more commonly seen.<sup>9, 16</sup>

Serologic findings show a 90% prevalence of ANA (antihistone and anti-single-stranded DNA antibodies specifically) and is characterized by the absence of anti-double-stranded DNA antibodies (seen in SLE) except in cases of penicillamine-induced SLE-like syndrome which is believed, as mentioned before, to cause an unmasking of latent SLE.<sup>9, 25, 26</sup> Other laboratory abnormalities can include elevated sedimentation rate, mild anemia and leukopenia.<sup>24</sup> Serum complement levels tend to remain normal.<sup>24</sup> Most patients with this condition have been found to have a slow acetyl transferase activity (slow acetylators) thus being more predisposed to becoming sensitized to the drug as compared with the fast acetylators.<sup>9, 24</sup> The histologic picture of cutaneous lesions in drug induced SLE-like syndrome is the same as in SLE, with IgG and IgM occasionally found in the dermoepidermal junction.<sup>16, 21</sup> A positive lupus band test upon direct immunofluorescence of normal-appearing skin is uncommon.<sup>16</sup>

Treatment of drug-induced SLE-like syndrome consists of withdrawal of the offending drug, in most cases followed by a complete resolution of the symptoms.<sup>21</sup> Humoral antibodies (ANA) persist for an average of four months after resolution of the symptoms,<sup>23</sup> but may also persist up to several years after the drug has been discontinued.<sup>24</sup> Despite the relatively benign course of the patients having a drug-induced SLE-like syndrome, death can occur in a few cases most often secondary to renal involvement.<sup>16</sup>

### Vesiculobullous eruptions

Various drugs may cause vesiculobullous eruptions clinically, histologically, and often immunologically indistinguishable from the primary vesiculobullous diseases. These diseases include pemphigus, pemphigoid, porphyria cutanea tarda, erythema multiforme (EM) and toxic epidermal necrolysis (TEN). EM and TEN will be discussed separately.

Drugs that induce pemphigus-like eruptions include d-penicillamine, captopril, piroxicam, penicillin, rifampin, phenobarbital, thiopronine, and alpha-mercaptopyrionyl glycine.<sup>27</sup> D-penicillamine is responsible for most cases of drug-induced pemphigus and a pemphigus-like

eruption will occur in 3-10% of patients using this drug.<sup>27</sup> Pemphigus-like lesions have also been reported sporadically in patients using captopril.<sup>27</sup> The lesions usually resemble pemphigus foliaceus, but they may also resemble pemphigus vulgaris and pemphigus erythematosus. The skin lesions are clinically and histologically identical to those of pemphigus but circulating and tissue-bound autoantibodies are often absent.<sup>28</sup>

The mechanism by which pemphigus-like eruptions are induced is still unknown. Penicillamine and captopril are drugs with similar chemical structures that contain highly reactive sulfhydryl residues. It is possible that these drugs may, in the absence of auto-antibodies, directly induce acantholysis by forming complexes with the pemphigus foliaceus antigen (desmoglein I, a desmosomal core protein) and the pemphigus vulgaris antigen via disulfide bonds and thus mechanically interfere with the cell to cell adhesion function of these antigens.<sup>28</sup> These two drugs may also induce true pemphigus lesions through a type II hypersensitivity mechanism in which the drug binds the above-mentioned antigens forming a new antigen that will be recognized by autoantibodies.<sup>28</sup> The lesions of drug-induced pemphigus usually resolve spontaneously with discontinuation of the drug but up to 30% of patients will require aggressive corticosteroid or immunosuppressive therapy and some deaths have been reported.<sup>27</sup>

There has been one report of bullous pemphigoid induced by furosemide in which the lesions resolved with discontinuation of the medication and recurred with rechallenge.<sup>29</sup> There are scattered reports of other drugs causing bullous pemphigoid-like lesions which appear to represent coincidental findings.<sup>30</sup> There is one report of a cicatricial pemphigoid-like eruption attributed to clonidine.<sup>31</sup>

Porphyria cutanea tarda (PCT)-like eruptions may be precipitated by nalidixic acid,<sup>32</sup> tetracycline,<sup>33</sup> and furosemide.<sup>34</sup> These differ from true PCT in that porphyrin levels in blood, plasma, urine, and feces are completely normal. Patients on hemodialysis can also develop PCT-like eruptions.<sup>35</sup>

### Erythema multiforme

Erythema multiforme (EM) is an acute self-limited inflammatory disorder of the skin and mucous membranes characterized by the presence of iris or target lesions. Adults in the second and third decade are predominantly involved, while the condition is rarely seen in patients younger than 3 years-old or older than 50 years-old. Males are affected in 60% of the cases.<sup>36</sup> Occasionally EM presents a seasonal variation, especially when herpes simplex is considered to be the etiologic agent.

There is an astonishing list of etiologic factors associated with EM but in only few instances has there been convincing evidence for a direct link between the etiologic factor and EM. The etiologic factors most thoroughly studied and closely linked to EM are herpes simplex virus infections and mycoplasma pneumonia.<sup>37</sup> Among other causes of EM drugs have been frequently associated with this condition. Long-acting sulfonamides have been extensively documented.<sup>3</sup> Drugs which have shown recurrent EM upon rechallenging include rifam-



picin, phenolphthalein, sulfapyridine and trimethoprim-sulfamethoxazole.<sup>24</sup> In 1990, Chan et. al.<sup>38</sup> reported the drugs most frequently implicated in 61 patients with EM and Stevens-Johnson syndrome requiring hospitalization. These were, again, sulfamethoxazole and trimethoprim, phenobarbital and aminopenicillins (ampicillin and amoxicillin). Other drugs which have been associated with EM include ketotifen,<sup>39</sup> hydantoins, nonsteroidal anti-inflammatory agents (although several authors have mentioned the low risk of EM in comparison with the large consumption of these agents),<sup>38</sup> tetracycline and others.

Clinically EM can present with various types of skin lesions which include erythematous macules and papules, vesicles, bullae and urticarial plaques. Clinical manifestations of EM can be framed into three different presentations.<sup>37</sup> First, there is a papular or simplex form which is characterized by the presence of erythematous macules and papules, mainly localized to the palms, dorsal aspect of the hands, extensor surface of the wrists and forearms, feet, elbows and knees, with less frequent involvement of the face and neck. These papules will increase in size centrifugally acquiring the characteristic target appearance (iris, bull's eye) with a peripheral erythematous ring and a purpuric or violaceous center (Figure 4). Second, there is a vesiculo-bullous presentation in which erythematous urticarial plaques with a central bulla and a marginal ring of vesicles (herpes iris) are present. Bullae tend to appear over urticarial plaques or over an erythematous base. There are relatively fewer lesions compared with the papular form but mucous membranes can be involved. Third, there is a severe bullous form (Figure 5) also known as erythema multiforme major or Stevens-Johnson syndrome (SJS). EM major is usually preceded by a nonspecific prodrome lasting from one to fourteen days, presenting with severe constitutional symptoms of fever, malaise, cough, sore throat, chest pain, vomiting, diarrhea, myalgias and arthralgias.

Drug-related cases of EM typically begin within three weeks of initiation of the drug. If the patient has been previously exposed to the drug, the reaction may begin within hours of restarting the agent. The prodrome is followed by a sudden onset of vesicle and bullae formation, involving the mucous membranes of the oral mucosa, lips, eye, pharynx, respiratory tract, vagina and glans penis. These bullae break, leaving a white-gray pseudomembrane with hemorrhagic crusts. Oral involvement can cause difficulty in swallowing, with subsequent malnourishment. Genital involvement can lead to vulvovaginitis, balanitis with secondary urine retention, phimosis, and cicatrizing bands in the vagina.<sup>36</sup> Ocular complications can include conjunctivitis, anterior uveitis and panophthalmitis. Secondary infection may lead to corneal opacities, synechiae and blindness. Other complications include bronchopneumonia, anemia, renal failure, and water and electrolyte imbalances.

EM is believed to be a hypersensitivity reaction most probably mediated by immune complexes.<sup>16</sup> Histopathologic evaluation of cutaneous lesions will help establish the diagnosis of EM but is of no help in identifying the precipitating agent.<sup>16</sup>

The differential diagnosis of EM includes chronic



Figure 4. Acrally distributed iris lesions of erythema multiforme.



Figure 5. Stevens-Johnson Syndrome.

urticaria, pemphigus, bullous pemphigoid, serum sickness, dermatitis herpetiformis and drug eruptions among others, depending on the specific clinical presentation.

Management of localized EM is mainly symptomatic with emphasis in eradicating the etiologic agent or discontinuing the offending drug. The treatment of widespread disease or EM major consists of good nursing care, optimal ophthalmologic care to prevent ocular sequelae, and close monitoring of fluid and electrolyte status. Therapy with systemic corticosteroids remains controversial. Some authors think that systemic corticosteroids will provide a symptomatic relief to the patient, but there is no conclusive evidence that corticosteroid therapy reduces the mortality in EM.<sup>37</sup> In fact, studies have shown that steroid therapy in SJS has been associated with a greater frequency of complications.<sup>40</sup> Recurrences, often of greater severity may occur with reexposure to the offending agent. SJS is more severe and is associated with a mortality of five to fifteen percent.

#### Toxic epidermal necrolysis

Toxic epidermal necrolysis, also known as Lyell's syndrome, is a rare condition characterized by widespread skin erythema and scalding. Adult patients are predominantly involved and there is no racial or sex predilection.<sup>41</sup> Controversy still exists as to whether this condition is a more severe form within the erythema multiforme (EM) spectrum or whether it represents a clinical entity distinct from EM.<sup>42</sup> Indeed occasional cases of

Stevens-Johnson syndrome (SJS) have been reported to precede TEN.<sup>43</sup>

As in EM it is believed that immune mechanisms are involved in the pathogenesis of TEN. Out of several etiologic factors associated with TEN, drugs are the most frequently involved. A review of 87 patients who were hospitalized with a diagnosis of TEN showed the following drugs to cause TEN in decreasing order of frequency: nonsteroidal anti-inflammatory agents (especially phenylbutazone derivatives and oxicam derivatives), sulfonamides (especially sulfamethoxazole and trimethoprim), anticonvulsants (barbiturate and carbamazepine), allopurinol, and chlormezanone.<sup>44</sup> Other drugs reported to be associated with TEN are cephalixin and cephmandole,<sup>45</sup> rifampin,<sup>46</sup> dilantin,<sup>47</sup> fenoprofen and other propionic acid derivatives such as naproxen, ibuprofen and benoxaprofen,<sup>47</sup> penicillin,<sup>41</sup> tetracycline<sup>41</sup> and others (see Table I).

TEN presents with an acute prodrome characterized by fever, burning sensation of the conjunctiva, skin tenderness, malaise and arthralgias followed by a morbilliform rash which can progress to confluent erythema with a pale hue. There will be vesiculation forming large flaccid bullae which break at pressure points. Nikolsky's sign (referring to sheetlike removal of the epidermis by gentle traction with the finger) is positive only in areas of erythema. There can be loss of the epidermis in up to 50% or more of the body surface. There is also an extensive mucosal involvement of the lips, oral mucosa, conjunctivae, and anal and genital areas which may lead to complications similar to those described previously for SJS. Other complications include water and electrolyte imbalances, albuminuria, renal failure, pulmonary edema, bronchopneumonia, gastrointestinal hemorrhage, shock, secondary infections and sepsis.

Goldstein et al<sup>42</sup> proposed a set of diagnostic criteria for the diagnosis of TEN which include the following: widespread blistering with morbilliform or confluent erythema and associated skin tenderness, the absence of target lesions, sudden onset and generalization within 24 to 48 hours, and characteristic histologic findings.

The differential diagnosis of TEN includes EM, staphylococcal scalded skin syndrome, generalized fixed drug eruption and toxic shock syndrome.

Therapy of TEN, again mainly relies mainly on discontinuation of the offending drug and symptomatic treatment which includes good nursing care, optimal ophthalmologic care fluid and electrolyte monitoring and treatment of secondary infections.<sup>41, 43</sup> With respect to systemic corticosteroid therapy, Revuz et al<sup>40</sup> mention that the benefit of steroid therapy, if any, would only be seen at an early stage of the disease and emphasize that if more than 20% of the body surface area is scalded, the supposed advantages of steroid therapy will be neglected by its potential side effects. Still, others argue in favor of high dose systemic corticosteroid therapy.<sup>41</sup> Plasmapheresis has been reported to be useful in several cases of TEN.<sup>40</sup>

The prognosis of TEN is worse when compared with EM. The mortality in patients affected with TEN has been estimated to range from twenty-five to fifty percent.<sup>40, 41</sup> Three factors have been found to be important variables

in terms of prognosis: age of the patient, the percentage of denuded skin and the blood urea nitrogen level.<sup>48</sup> Causes of death in TEN include sepsis, gastrointestinal hemorrhage, fluid and electrolyte imbalances and pulmonary embolism.<sup>41, 48</sup>

### Pigmentary changes

Drugs may produce changes in cutaneous pigmentation by various mechanisms. The drug itself may act as a pigment when deposited in the skin. Alternatively, the drug may have direct or indirect effects on the amounts of the cutaneous pigments responsible for normal skin color, namely, melanin, carotene, oxyhemoglobin, and reduced hemoglobin. The skin color perceived by an observer will depend on the true color and location of the various pigments. In many cases, the exact mechanism by which the cutaneous pigmentary change is produced is not known.

Heavy metals can result in pigmentation by being deposited in the skin. Some such as silver, mercury, and iron also stimulate melanin synthesis by either increasing oxidative processes or by binding sulfhydryl groups on epidermal cells.<sup>16, 49</sup> Prolonged administration of gold can result in a blue-gray pigmentation of the sun-exposed area (chrysiasis). A similar cutaneous pigmentation in addition to discoloration of the conjunctiva and oral mucosa can result from the systemic use of silver salts (argyria). Silver in some nose and eye drops and in silver sulfadiazine cream may result in pigmentation localized to the area of application.<sup>50</sup> Other heavy metals such as lead, mercury, bismuth, and titanium may produce characteristic pigmentary changes.<sup>50</sup> Histopathologic examination of the affected skin is often diagnostic.<sup>16</sup>

Inorganic arsenic (Fowler's solution) used in the past for the treatment of psoriasis causes a diffuse macular bronze pigmentation of the trunk and extremities. It is thought that arsenic binds sulfhydryl groups in epidermal cells causing an increase in tyrosinase activity and consequently an increase in melanin synthesis.<sup>52</sup>

Phenothiazines, especially chlorpromazine, cause a slate-gray pigmentation most prominent in sun-exposed areas in some patients receiving high doses for prolonged periods of time. Chlorpromazine may also cause a brownish coloration of the exposed bulbar conjunctiva and deposition of a melanin-like material in multiple internal organs. It is thought that chlorpromazine is deposited in the dermis where it binds to melanin forming a chlorpromazine-melanin complex that then enters the circulation and is subsequently deposited in the various internal organs.<sup>53</sup>

Lichenoid drug reactions, fixed drug eruption, and other inflammatory drug reactions may resolve with residual brown pigmentation (postinflammatory hyperpigmentation) as previously discussed.

Minocycline, a semi-synthetic tetracycline, may cause three types of pigmentary changes which may occur together or independent of each other. These include a blue-black pigmentation in areas of scars, a blue-gray pigmentation at "normal" skin areas usually involving the legs and forearms, and a diffuse, muddy brown discoloration. The first two probably occur through a mechanism similar to that of chlorpromazine in which



drug metabolite-melanin complexes are formed whereas the third probably represents postinflammatory hyperpigmentation.<sup>16</sup>

Amiodarone, a drug used for the treatment of arrhythmias, is known to cause a slate-gray pigmentation of sun-exposed areas similar to that of argyria as well as a blue-red coloration of the hands and feet. These pigmentary changes, which have been estimated to occur in 10% of patients using this medication, usually occur in those with prolonged use of high daily doses (usually more than 400mg/day).<sup>16, 50</sup>

Oral contraceptives, ACTH, and hydantoin derivatives may induce a melasma-like pigmentation. The exact mechanism of how this occurs is not clear.

A yellowish, diffuse pigmentation may result from use of carotenes, lycopenes, antimalarials, and nitro compounds. Carotenes, a carotenoid pigment found in carrots, squash, pumpkin, and other vegetables, cause a diffuse canary-yellow discoloration which spares the sclera and mucous membranes. Lycopenes, another type of carotenoid pigment which is found in tomatoes and beets, produce a diffuse yellow-orange color most marked in the palms, soles, forearms, and face. Almost all patients on quinacrine will develop a lemon-yellow discoloration that fades 1-2 months after stopping the drug. Nitro compounds such as analine dyes and picric acid may cause a localized or diffuse yellowish discoloration that may involve the sclera thus mimicking jaundice. Whenever localized yellowish discoloration is found, a history of contact with a nitro-containing compound should be sought.<sup>50</sup>

Clofazimine (Lamprene), a drug used in the treatment of leprosy, produces a diffuse reddish-blue pigmentation within two weeks of onset of therapy and a perilesional brown pigmentation within the next few months of treatment in most patients. The former may be due to deposition of the drug itself in the subcutaneous tissue,<sup>50</sup> and the latter may be due to stimulation of melanin synthesis,<sup>50</sup> or a drug-induced ceroid lipofuscinosis.<sup>51</sup> Methylsergide may also produce a transient reddish discoloration of the skin.

The chemotherapeutic agents and multiple other drugs may also cause characteristic cutaneous pigmentary changes. These have been extensively reviewed in other articles to which the reader is referred for further information.<sup>11, 50</sup>

### Approach to the patient

The diagnosis of a cutaneous drug reaction rests mainly on the history and clinical findings as there is no readily available test to directly implicate a given drug as the cause of a given reaction. Important facts to elicit from the history include the timing of the onset of the reaction with respect to the administration of the suspected offending agent, dosage of the medication, associated symptoms, and a previous history of similar reactions. Recognition of a given cutaneous reaction pattern will help to further limit the diagnostic possibilities. Rechallenge could theoretically help confirm that a reaction is due to a given drug, but it may cause significant morbidity or mortality.

Once the diagnosis of a cutaneous drug reaction is

made, one must determine whether it is immunologic or nonimmunologic in origin. An immunologic origin of a drug reaction is suggested by the following: (1) the reaction is not a pharmacologic effect of the drug; (2) the reaction is of a morphology associated with allergic drug reactions, e.g., urticaria or EM; (3) the reaction may occur with very small doses of the drug; (4) the reaction reappears with period following initial administration of the drug; (5) the reaction reappears with rechallenge, (6) the reaction is associated with other signs and symptoms of allergy, and (7) there is cross-reaction with structurally similar drugs.<sup>1, 3</sup>

Laboratory tests usually are not helpful in diagnosis as there are no specific findings. Presence or absence of peripheral eosinophilia is of little value in excluding or confirming the diagnosis.<sup>54</sup> Laboratory findings may be helpful in detecting effects of the drug in organs other than the skin.

Microscopic examination of biopsies of affected skin is often helpful in confirming the diagnosis. As previously mentioned, histologic findings will help establish the diagnosis of a given morphologic variant and help exclude other possibilities, but will not differentiate among the different causes of the given morphologic pattern. In the case of cutaneous changes due to heavy metal deposition, the histopathologic findings are characteristic.<sup>16</sup>

There are no readily available tests for establishing the diagnosis of a drug reaction. Various in vitro and in vivo assays may help detect drug-specific immune responses, but these can only be used if the responsible antigens are known which is not the case with most drugs. Prick or intradermal tests for drug allergies are reliable with drugs such as penicillin, antisera, hormones, vaccines, and enzymes; they are not reliable with other drugs. In the case of penicillin, skin testing is of greater value than medical history in prevention of serious penicillin reactions.<sup>3</sup> Tests for delayed hypersensitivity, such as patch tests and photopatch tests, are rarely helpful in the case of systemic drugs. The radioallergosorbent test (RAST), a quantitative assay used to determine drug-specific IgE, has been used in the study of penicillin allergies, but it has been of no use with other drugs as the involved antigenic determinants are unknown. Other tests with the same problems include those measuring lymphocyte transformation, formation of immune complexes in vitro, and lymphokine production.<sup>1</sup>

Treatment of drug reactions involves cessation of the culprit drug and supportive care. The extent of the supportive care will depend on the type and severity of the reaction. Severe and life-threatening reactions such as TEN and anaphylaxis may require therapeutic intervention. In cases where the reaction is associated with only mild morbidity, but the drug cannot be adequately substituted, one may have to continue therapy. Clearly, the patient must be instructed as to the implications of the drug reactions and as to any possible cross-reactions.

**Resumen:** Las reacciones cutáneas a medicamentos constituyen unas de las causas más comunes de erupciones en piel en pacientes hospitalizados. En clínicas ambulatorio-

rias, las dermatitis medicamentosas representan un reto clínico terapéutico para el médico, ya que cualquier droga puede ocasionar una reacción adversa cutánea. Estas dermatosis pueden ser mediadas por respuestas inmunológicas y no inmunológicas a la sustancia. Factores, tales como exposición solar, drogas o enfermedades concomitantes y el estatus inmunológico del paciente pueden influenciar el tipo y la morfología de las lesiones.

El historial constituye uno de los aspectos más importantes en la evaluación de estos pacientes y se debe realizar de tal manera que nos provea la información más relevante que nos conduzca hacia un diagnóstico final.

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## CME QUIZ

- Which of the following has been most thoroughly documented as an etiologic agent in erythema multiforme:
    - drug therapy
    - collagen disease
    - herpes simplex
    - X-radiation
    - internal malignancies
  - Which of the following drugs are commonly associated with drug-induced systemic lupus erythematosus:
    - hydralazine
    - dilantin
    - procainamide
    - none of the above
    - all of the above
  - All of the following are true of toxic epidermal necrolysis except:
    - drugs are the most frequent etiology
    - pathogenesis is thought to be of immunologic origin
    - characteristic skin scalding
    - Nikolsky's sign is negative
  - Acneiform eruptions may be induced by all of the following except:
    - corticosteroids
    - dilantin
    - INH
    - lithium
    - aspirin
  - Coumadin necrosis is characterized by the following except:
    - lesions tend to appear within the first two weeks of treatment
    - males are more frequently affected than females
    - patients are usually obese
    - patients are usually middle-aged
    - areas most commonly involved are those with abundant subcutaneous fat
  - Drugs that may directly cause degranulation of mast cells include the following except:
    - opiates
    - aspirin
    - dilantin
    - d-tubocurarine
    - polymyxin B
  - The most important histologic finding to help differentiate lichenoid drug eruptions from true lichen planus is:
    - Wickham's striae
    - vacuolar alteration of the basal layer
    - lymphohistiocytic infiltrate
    - eosinophilic infiltrate
    - drug deposition in dermis
  - Drugs associated with fixed drug eruptions include all of the following except:
    - sulfonamides
    - nonsteroidal anti-inflammatory drugs
    - prednisone
    - barbiturates
    - phenolphthalein
- For each drug, select the skin discoloration most closely associated with it.
- |                              |                            |
|------------------------------|----------------------------|
| _____ 9. oral contraceptives | a. slate-gray pigmentation |
| _____ 10. gold               | b. red pigmentation        |
| _____ 11. methylsergide      | c. yellow pigmentation     |
| _____ 12. quinacrine         | d. brown pigmentation      |



## Hoja de Registro CME



Initial Evaluation of the  
Asthmatic Patient  
Correct Answers

- |      |       |
|------|-------|
| 1) c | 6) c  |
| 2) b | 7) b  |
| 3) d | 8) c  |
| 4) a | 9) d  |
| 5) a | 10) d |

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# CASE REPORTS

## Thrombotic Phenomena in the Presence of A Circulating Anticoagulant

Aida L. Quintero, MD  
Aida Lugo-Somolinos, MD  
Jorge L. Sánchez, MD

In 1963, Bowie was the first to recognize and correlate the paradox of thrombotic phenomena in the presence of a circulating anticoagulant.<sup>1</sup> The report consisted of eleven patients with systemic lupus erythematosus (SLE) in whom the presence of lupus anticoagulant (LA) was corroborated in eight of them. Four of them presented thrombotic problems which included deep vein thrombosis and leg ulcers. Since then, multiple reports have followed associating the presence of LA with venous and arterial thrombotic processes in patients with SLE,<sup>2, 3, 4</sup> other autoimmune disorders,<sup>5, 6</sup> and neoplasms.<sup>6</sup> In 1975, Nilsson described LA associated with intrauterine death and recurrent abortions adding to the clinical spectrum associated with this factor.<sup>7</sup>

This is a report of a patient with hyperthyroidism who developed signs and symptoms of thrombotic phenomena in the presence of a circulating anticoagulant.

### Case Report

This is the case of a 14-year-old female patient with history of hyperthyroidism since 4 years ago who was being treated with propylthiouracil (PTU) for approximately 1 1/2 years. The patient was doing well until 9 days prior to admission to the hospital when she developed small purpuric lesions on the lower extremities. These lesions were more prominent on the acral areas. In the days that followed, new lesions appeared involving the forearms, some of which developed vesicles. PTU was discontinued due to the suspicion of a drug vasculitis. There was no history of fever, bleeding, recent infection, diarrhea, vomiting, hematuria or dysuria. Past and family history were non-contributory.

Physical examination revealed an afebrile, alert patient who presented bright, red-wine ecchymotic plaques with small vesicles on the borders, localized symmetrically on the flexor aspects of the forearms. On the distal third of the legs, also symmetrically, there were red-wine plaques with bulla formation. (Figure 1).

Laboratory studies showed a white blood cell count of 4,400/mm<sup>3</sup>; a hemoglobin of 10.9gm/dl and a platelet count of 293,000. Prothrombin time was 11 sec/11 sec,



Figure 1. Ecchymotic red-wine plaques with necrosis seen in the distal third of both legs.

and the partial thromboplastin time (PTT) was 30 sec control, 56 sec patient. Antinuclear antibodies (ANA) showed a positive speckled pattern and the anticardiolipin antibodies were reactive. Direct and indirect Coomb's, VDRL, LE cell prep, Protein C and Protein S levels were normal.

A skin biopsy from one ecchymotic plaque showed thrombosis of the superficial vascular plexus with a sparse perivascular mononuclear cell infiltrate and focal epidermal necrosis.



The skin lesions healed leaving atrophic scarring and no new lesions appeared.

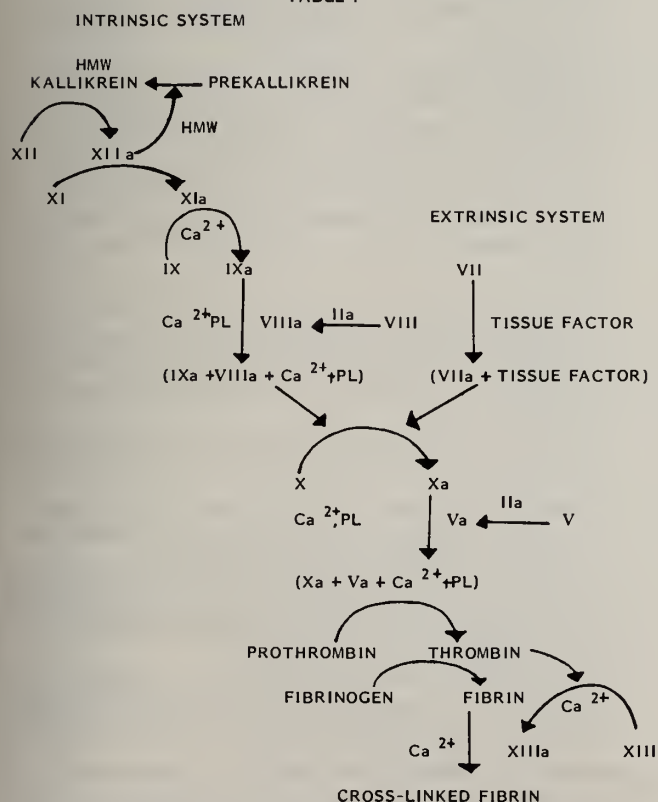
### Discussion

Lupus anticoagulant (LA) is defined as a group of heterogenous immunoglobulins which prolong the *in vitro* phospholipid dependent coagulation tests without inhibition of specific coagulation factor activity.<sup>8</sup> These immunoglobulins may be of the IgG type, IgM type or mixed forms (IgG, IgM),<sup>9</sup> all interacting with phospholipid dependent coagulation tests.

It was first described in 1952 by Conley and Hartmann<sup>10</sup> who reported a spontaneous acquired circulating agent in a patient with systemic lupus erythematosus (SLE). This circulating agent, *in vitro*, interferes with the formation of prothrombin activation complex, which develops from the interaction of Factors Xa, V, calcium and phospholipid.

The coagulation system is composed of the intrinsic and extrinsic pathways that meet at the Factor X level (Table I). The intrinsic pathway is activated by several stimuli including collagen exposure, bacterial toxins, cartilage, trypsin, and kallikrein. The extrinsic pathway is activated by tissue factors. The human body maintains a dynamic balance between coagulation-anticoagulation mechanisms. The most important factors contributing to the no thrombogenicity of the blood vessel wall include:

TABLE I



Cascade mechanism of blood coagulation.

an intact plasma membrane, prostacyclin synthesis (which is a vasodilator and potent platelet aggregation inhibitor), secretion of tissue plasminogen activators, neutralization of thrombin and activation of protein C.<sup>8</sup>

Multiple mechanisms of action have been proposed suggesting that the exact pathogenesis is not clearly defined. It has been proposed that LA inhibits prostacyclin production by endothelial cells causing platelet aggregation and vascular thrombosis.<sup>11, 12</sup> In 1981, Carreras et al<sup>11</sup> studied 14 patients with LA and found that LA interferes with the availability of arachidonic acid to the cellular membrane. A more recent study by Dudley et al<sup>13</sup> did not confirm these findings. They studied the effect of antiphospholipid antibodies on prostacyclin production by damaged endothelium *in vitro*. They concluded that prostacyclin production is not impaired by sera containing antiphospholipid antibodies regardless of the endothelial integrity.

Another theory proposes an imbalance in the coagulation system due to fibrinolysis inhibition.<sup>14</sup> The authors postulated that a decrease in prekallikrein, which is a proactivator in plasminogen activation, causes a decrease in fibrinolysis.

A decrease in protein C activation may also be involved in this phenomenon. Protein C is a seric esterase which is activated by thrombin-thrombomodulin complex in the presence of calcium and phospholipid. Freyssinet et al.<sup>8</sup> demonstrated that incubation of thrombomodulin, phospholipids and inactive protein C in the presence of patient serum with LA inhibits activation of protein C. They suggest that phospholipid neutralization by LA can reduce protein C activation causing thrombotic complications.

Antiphospholipid action is a common variable among the theories proposed to explain the mechanism of action of lupus anticoagulant. Due to the heterogeneity of LA, its specificity may vary. The ubiquitous presence of phospholipids in cell walls and their various roles in the coagulation process as well as the variable specificity of LA suggest that more than one mechanism occurs at the same time.<sup>15</sup>

Initially, most of the studies were done in SLE patients due to the fact that LA was first described in association with this condition. Because the patients with SLE have numerous other clinical and laboratory manifestations that are related to autoantibodies or derangement other than antiphospholipid antibodies, the relationship between clinical manifestations and pathogenetic role of these antibodies is difficult to ascertain.<sup>15</sup> The recognition and study of patients with LA associated to other autoimmune diseases, neoplasms, exposure to drugs and even to the idiopathic syndrome<sup>16</sup> gave support to the role of these immunoglobulins in the pathogenesis of these clinical findings.

Thrombosis is the most characteristic clinical manifestation and occurs in 23-58% of the cases.<sup>9</sup> Venous thrombosis is more frequently reported with deep vein thrombosis being the most common presentation.

Obstetric complications presenting as intrauterine death and recurrent abortions is another common clinical manifestation.<sup>7</sup> LA adhesion to placental phospholipid, inhibiting its growth or nutrient transfer,

and/or vascular thrombosis due to decreased prostacyclin production may explain these complications.<sup>12, 17</sup>

Central nervous system manifestations have been proposed to be due to LA cross-reactivity with cerebral phospholipids.<sup>18</sup> They include migraine,<sup>16</sup> chorea<sup>19</sup> and epilepsy.<sup>20</sup>

Other manifestations include thrombocytopenia<sup>16</sup> and hemolytic anemia.<sup>21</sup>

Cutaneous manifestations associated with LA have been documented in case reports although large studies are not available. Livedo reticularis, leg ulcers, distal ischemia and necrosis are among the prominent cutaneous signs seen in these patients.

Livedo reticularis is defined as a persistent reticulated pattern which may occur on the extremities or trunk.<sup>22</sup> In 1987, Weinstein<sup>23</sup> studied 78 SLE patients and found a statistically significant association between the presence of moderate to severe livedo reticularis, anticardiolipin antibodies and central nervous system or renal disease. He concluded that livedo reticularis may represent a cutaneous marker for a SLE subset prone to develop serious systemic involvement.

Although direct studies correlating leg ulcers and LA have not been performed, the finding that 7% of 110 patients with false positive VDRL have leg ulcers suggests that antiphospholipid antibodies have a pathogenic role in these lesions.<sup>24</sup> Grob et al<sup>9</sup> reported a 44 year-old female with SLE and LA presenting leg ulcers in whom a venography showed sequelae of deep venous thrombosis.

Other cutaneous manifestations that have been linked with LA but with less evidence include Dego's disease<sup>25</sup> and Behcet's disease.<sup>26</sup> In 1980,<sup>27</sup> it was seen that LA IgM type, which was present in a patient with macroglobulinemia, inhibited specifically the anionic phospholipids, causing a prolongation of the PTT that reversed to normal when platelets were used. PTT was done taking the patient plasma and a platelet substitute (which is a phospholipid) proposing then that LA inhibited the substitute but not the platelets in vivo. The same authors,<sup>28</sup> in 1987, studied the immunologic specificity and LA mechanism of action to reconfirm their theory and found that LA IgG type reacts with the anionic phospholipids inhibiting the interaction of prothrombin and Factor X in phospholipid covered vesicles. They concluded that LA is a group of antibodies with specificity to anionic phospholipids blocking the interaction of coagulation factors to phospholipid surfaces. Although other authors have been unable to confirm these findings, these differences have been explained due to the heterogeneity and variable specificity of LA.

The differential diagnosis of LA includes purpura fulminans, Coumadin fat necrosis, and Protein C and Protein S deficiencies.

Purpura fulminans has an acute onset, is usually fatal and clinically presents with irregular symmetric ecchymoses on the extremities.

Coumadin fat necrosis is a rare condition which occurs 3-5 days after Coumadin therapy. The clinical picture presents with tenderness on the thighs, buttocks or breasts that progresses to erythematous patches and hemorrhagic bullae leaving necrosis and eschar.<sup>29</sup>

Protein C deficiency is transmitted as an autosomal trait. The inherited form has variable penetrance and the clinical manifestations includes fatal purpura in the homozygous patient and recurrent thrombophlebitis<sup>29</sup> in the heterozygous patients. Acquired dysfunction of the protein C system has also been associated with thrombotic episodes.<sup>29</sup>

Protein S is a vitamin K-dependent protein with no enzymatic activity. It forms a complex with activated protein C on phospholipid vesicles causing a tenfold increase in the inactivation of factor Va by protein C. The deficiency of this protein interferes with the optimal function of protein C explaining the thrombotic tendency. Patients with LA and recurrent thrombotic episodes have been treated with long term anticoagulant therapy. Treatment of females with recurrent abortions and LA with prednisone might increase the chance of live births.<sup>30</sup> Recently the use of more aggressive therapy including immunosuppressives and plasmapheresis has been in debate.<sup>31</sup>

In summary, lupus anticoagulant syndrome is a syndrome caused by heterogeneous antiphospholipid antibodies, presenting clinically with thrombotic episodes, obstetric complications, and neurologic manifestations.

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## Lupus Pernio

Gerardo Lugo-Janer, MD

**L**upus pernio (LP), described by Besnier in 1889,<sup>1</sup> represents an unusual but specific cutaneous manifestation of sarcoidosis. It manifests itself as diffuse, violaceous to telangiectatic lesions on cold sensitive areas such as the nose, cheeks, ears, and fingers. Discrete, small papular to nodular lesions at the nasal rim are also included under this designation.<sup>2</sup>

LP has been commonly associated with lesions of the upper respiratory tract (URT) and progressive fibrotic changes in the lung.<sup>3</sup> This is a report of a patient with LP and sarcoidal lung disease which illustrates the importance of excluding respiratory system involvement in patients with this cutaneous manifestation of sarcoidosis.

### Case Report

A 54-year-old white female presented with a 2 year history of erythematous discoloration and disfigurement of her nose. Eight months prior to her evaluation, a skin biopsy performed elsewhere was reported as acne rosacea with granulomatous reaction. She was treated with oral tetracycline and topical sodium sulfacetamide and sulfur. As she saw no improvement and began to develop difficulty in breathing, she sought a second opinion. She had

no known systemic disease and was taking no other medication.

Examination of the skin showed diffuse erythema and telangiectases on the distal two-thirds of the nose. The anterior nasal rim presented erythematous infiltrated papular lesions. Just below the right nostril there were three flat-topped erythematous infiltrated papules (Figure 1). No surface changes were noted. Lymph nodes were not enlarged. Examination revealed that the heart was normal. Auscultation of the lungs revealed fine rales on the lower right base. Neither the spleen nor the liver were palpable, but the liver was measured to be approximately 8.0 cm at the anterior axillary line by percussion. The rest of the physical examination was unremarkable.

The CBC, VDRL and urinalysis were within normal limits. The SMA-20 was WNL except a serum calcium level of 11.2 mg/dl. The serum angiotensin converting enzyme (SACE) was 60 U/L (normal 8-52). The 24 hr. calcium excretion, serum protein electrophoresis, sedimentation rate, ANA, and electrocardiogram were within normal limits.

Roentgenograms of the hands and feet were normal. The chest roentgenogram revealed a small cavitory lesion on the left upper field and increased interstitial markings.



Figure 1. Papular lesions on rim of the ala nasae and nasal vestibule.

The tuberculin test was negative. Pulmonary function studies were interpreted as moderate obstructive airway dysfunction, not improved after bronchodilators and mild to moderate decrease of CO transfer with mild hypoxemia and adequate acid-base status. The gallium scan was reported as: gallium-avid process involving both parahilar regions and right lung consistent with sarcoidosis.

Otolaryngologic and ophthalmologic evaluation revealed no evidence of sarcoidosis.

A punch biopsy was taken from a papule on the right nasal vestibule. Examination of hematoxylin-eosin sections showed a noncaseating granuloma within the dermis. Aggregates of epithelioid histiocytes, lymphocytes and numerous Langhans giant cells were present. No polarizable material was seen. Fite and Ziehl-Neelsen stains for acid-fast organisms were negative, as was a periodic acid-Schiff stain for fungi.

### Discussion

Sarcoidosis is a multisystemic disease of unknown etiology characterized by the formation of noncaseating granulomas. It can involve any organ of the body, but has predilection for the lungs, lymph nodes, skin, and eyes.<sup>3</sup> Skin manifestations occur in one-fourth to one third of the patients and can be separated into specific and non-specific manifestations.<sup>4</sup> Specific lesions are those that on biopsy reveal noncaseating granulomas. They are seen in 10-35% of the patients and are usually associated with an unfavorable prognosis.<sup>5</sup> Nonspecific lesions are those that fail to reveal granuloma formation but are associated with sarcoidosis in other systems. The principal example of a nonspecific lesion is erythema nodosum.

LP is one of the specific skin manifestations of sarcoidosis. It has an insidious onset, and once established, it rarely resolves.<sup>4</sup> Women in the fourth and fifth decade of life are primarily affected. Its manifestations range from a few small button-like papules or nodules on the nasal rim to exuberant plaques covering the nose and spreading across both cheeks. Lesions may also occur on the eyelids, ears, and fingers. Rarely, similar lesions on the arms, buttocks, and thighs have been seen in association with the more typical lesions on the face.<sup>5</sup> LP is associated with chronic fibrotic sarcoidosis in other systems, particularly in the upper respiratory tract (URT). In fact, it has been considered a marker of URT involvement.<sup>2</sup> Over fifty percent of those patients affected have significant sarcoidosis in the nasopharynx, larynx and nasal bones.<sup>6</sup> Nasal ulceration, septal perforation or obstruction, which cause difficulty in breathing may occur.<sup>3</sup> Sarcoidosis of the URT has been associated frequently

with chronic pulmonary involvement, uveitis, and bone lesions.<sup>7</sup> Most patients with LP have sarcoidal parenchymal lung involvement which tends to progress to fibrosis with impairment of gas exchange.<sup>7</sup>

Patients with LP, as those with sarcoidosis in general, need a thorough evaluation for systemic disease. The initial work-up should include complete skin examination, ophthalmologic evaluation, complete blood cell count, urinalysis, serum and urine calcium levels, electrocardiogram, chest roentgenograms, pulmonary function studies (including diffusion studies), bone films, and SACE levels. It has been suggested that even in asymptomatic patients with LP, direct and indirect laryngoscopy should be done as part of the initial evaluation.<sup>2</sup>

The treatment of LP will depend on the extent of systemic involvement. Intralesional corticosteroids and antimalarial agents can be used to maintain the disease under control. Topical corticosteroids are of limited value.<sup>8</sup> Systemic corticosteroids, methotrexate and chlorambucil are effective treatment for LP associated with systemic sarcoidosis, but relapses occur upon withdrawal of treatment. Allopurinol, antituberculous drugs, and levamisole have been tried with poor results.<sup>5</sup> Recently, isotretinoin has been used successfully in a few patients.<sup>7</sup>

Sarcoidosis remains an incompletely understood disease that requires management by an interdisciplinary team of experienced specialists. The cutaneous manifestations can often serve as markers of specific organ involvement, as well as indicators of prognosis.

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# CLINICAL STUDIES

## Efficacy of 1, alpha 25-Dihydroxyvitamin D (Calcitriol) in the Treatment of Psoriasis Vulgaris: An Open Study

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Jorge L. Sánchez, MD  
Lillian Haddock, MD

**Abstract:** Several reports have appeared in the literature suggesting that Vitamin D metabolites and analogues may be useful for the treatment of psoriasis. This is a report of an open study in which the efficacy of 1, Alpha-25-dihydroxyvitamin D (Calcitriol) is evaluated in cases of moderate to severe psoriasis. Study of ten cases showed moderate improvement in four when using calcitriol at a daily dose of 0.5 ug for a period of three months. All Vitamin D metabolites were within normal limits during and after the trial. Further trials with calcitriol as an adjuvant therapy to topical steroids or photochemotherapy, as well as the development of topical Vitamin D analogues may be the future of this novel therapeutic alternative for psoriasis.

Psoriasis is a chronic, recurrent papulosquamous disease of unknown cause, characterized by increased epidermal proliferation. A single effective treatment is not available, so several modalities, including topical corticosteroids, tars, anthralins, oral antimetabolites, oral retinoids and different regimens of ultraviolet light have been used.

1, alpha-25-dihydroxyvitamin D<sub>3</sub> (1,25-(OH)<sub>2</sub> D<sub>3</sub>) is the active form of Vitamin D<sub>3</sub>. It is synthesized in the kidney from its precursor 25-OH cholecalciferol and it has been shown that human fibroblasts and keratinocytes possess receptors for this hormone.<sup>1, 2</sup> 1, alpha-25 (OH)<sub>2</sub> D<sub>3</sub> inhibits the proliferation of fibroblasts and cultured keratinocytes and stimulates terminal differentiation.<sup>3</sup> Cultured psoriatic fibroblasts show a partial resistance to 1, alpha-25 (OH)<sub>2</sub> D<sub>3</sub><sup>4</sup> providing a possible explanation for the loss of regulation and differentiation of psoriatic skin.

Several reports showing the efficacy of 1, alpha-25 (OH)<sub>2</sub> D<sub>3</sub> (Calcitriol) in psoriasis have appeared recently in the literature.<sup>5-8</sup> This is a report of an open study in which the efficacy of this drug is evaluated in cases of moderate to severe psoriasis.

### Patients and Methods

Thirteen patients with moderate or severe psoriasis vulgaris seen in our Dermatologic Clinic were studied. There were five males and eight females with ages ranging from 21 to 67 years. All patients had long standing history of psoriasis and were refractory to conventional treatment. None had history of previous spontaneous remissions, hypercalcemia, hypercalciuria or renal disease.

Severity of psoriasis was determined by total area of involvement. Patients were classified as severe if they had more than 60% involvement and moderate if they had 33 to 65% involvement. Ten patients had moderate and three patients had severe involvement.

All patients discontinued previous medications one month prior to the beginning of the study. White petrolatum applied to psoriatic plaques twice a day was permitted. All patients were advised as to the nature of the study and informed consent was obtained.

The patients were treated with 0.5 ug of calcitriol orally at bedtime for three months. They were evaluated at the beginning of the study, two weeks, six weeks, twelve weeks after the beginning of the study and 30 days after discontinuation of the drug. They were instructed to consume a low calcium diet of less than 400mg/day and to record their intake for three days previous to the visit for calculation of calcium consumption.

Photographs and blood samples including complete blood cell count, SMA-20, 24-hour urine calcium, serum parathyroid hormone (PTH), 25-OH D<sub>3</sub> and 1, alpha-26-(OH)<sub>2</sub> D<sub>3</sub> were obtained at the beginning of the study and at six weeks, twelve weeks and thirty days after discontinuation of the drug. Serum and urine chemistries were done by conventional methods. Serum samples for 25 (OH) D<sub>3</sub> were analyzed by a competitive rat protein binding assay,<sup>9</sup> the serum 1, alpha-25 (OH)<sub>2</sub> D<sub>3</sub> by a non-equilibrium radioreceptor assay employing a lyophilized 1, alpha-25 (OH)<sub>2</sub> D<sub>3</sub> receptor, which is isolated from the intestinal cytosol of rachitic chicks using the 1, alpha-25-dihydroxy-vitamin D [<sup>3</sup>H] assay reagent system of Amersham.<sup>10</sup> For the PTH assay the Allédro Intact PTH Immunoassay System, a two site immunoradiometric assay (IRMA) for the measurement of PTH (1-84)

produced by the Nichols Institute was used.<sup>11</sup>

Drug response was regarded as excellent if the patient had 75 to 100% improvement from the first visit, good - 50-74% improvement; fair 25-49% improvement; poor - less than 25% improvement, and worse if deterioration occurred.

The Students pooled t - test to determine the significance of difference of group means was used.

### Results

Ten patients completed the study. Two patients were lost to follow-up one month after the beginning of the study.

Patient #9 developed exfoliative dermatitis one week after the beginning of the drug and was withdrawn from the study.

At the end of the trial, four patients showed good improvement (50-74% when compared to initial visit); 4 showed no change (less than 50% improvement); and two patients (20%) had deterioration of their condition. These two patients (#1 and #5) had severe involvement. None of our patients had a complete clearing of the psoriasis. (Table I)

Mild improvement was usually seen at six weeks after the administration of oral calcitriol. It consisted of decrease in the amount of scales and pruritus. Definite improvement was consistently seen at three months in those patients who responded. This consisted of almost complete disappearance of adherent scales; decrease in the thickness of the plaques and no development of new lesions.

No side effects were reported.

All patients tested had normal serum calcium and phosphate levels, 25 (OH) D<sub>3</sub> and PTH (Table II), two patients had elevated alkaline phosphatase and one patient had a low 1,alpha-25 (OH)<sub>2</sub> D<sub>3</sub> level (13 pg/mL) at baseline. These parameters remained within normal levels during the three month period. In the patient who initially had low serum 1,alpha-25 (OH)<sub>2</sub> D<sub>3</sub>, subsequent levels were 28 and 24 pg/mL during therapy and 25 pg/mL after one month of therapy. The initial low level was considered to be a spurious finding with no clinical explanation.

Table I

Patient No.	Sex	Age	Involvement at Beginning of Study	Degree of Improvement
1	F	63	70%	Worse
2	F	22	33%	Good
3	F	49	33%	Good
4	M	23	33%	Poor
5	F	49	66%	Worse
6	F	21	33%	Fair
7	M	35	90%	D/C*
8	M	67	35%	Poor
9	M	44	55%	D/C*
10	F	57	40%	Good
11	F	56	50%	Fair
12	F	37	35%	D/C*
13	M	39	50%	Good

Degree of improvement was classified as excellent >75% improvement, good from 50-75% improvement, fair from 25-50% improvement, poor less than 25%, and worse if deterioration occurred.

\*D/C means patient did not complete the study.

Figure 1 shows the mean and standard error of the mean (SEM) for the serum PTH; 1,alpha-25 (OH)<sub>2</sub> D<sub>3</sub>; the serum calcium and 25-OH D<sub>3</sub> at baseline, during

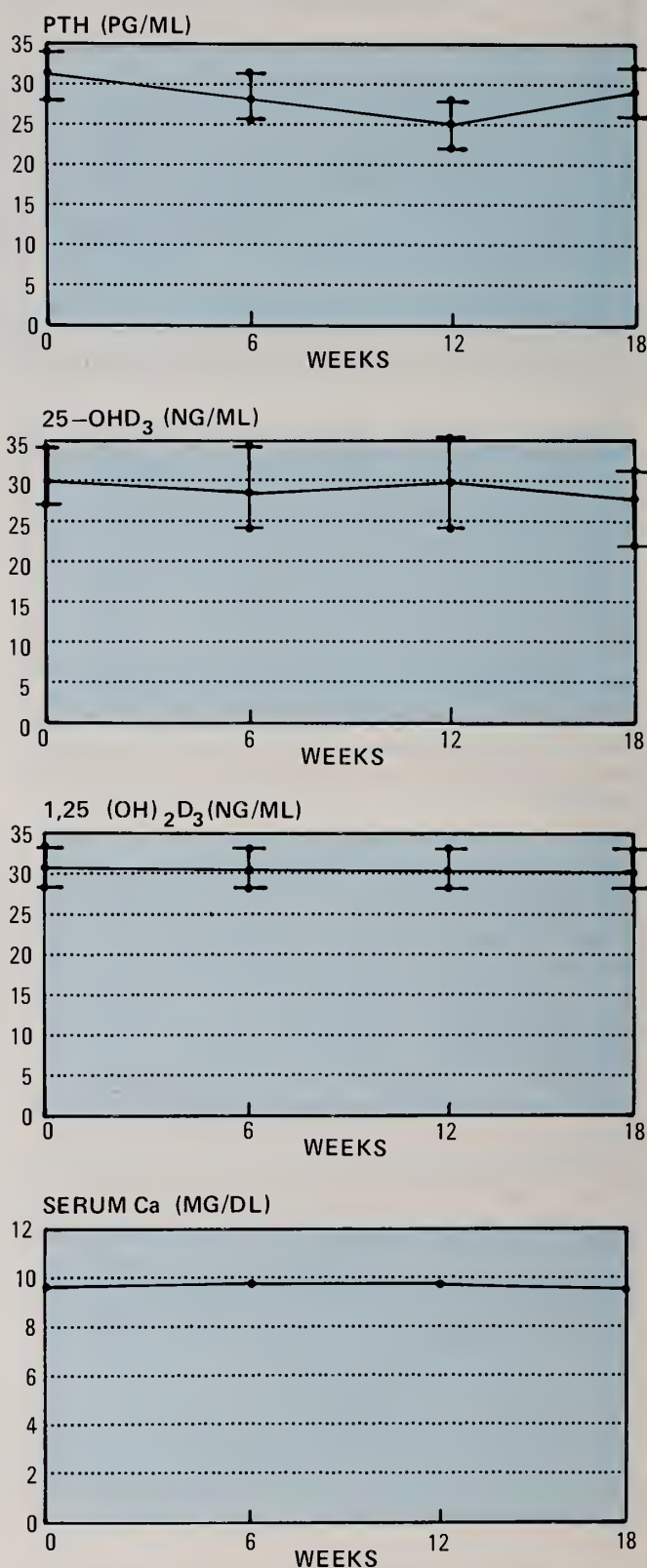


Figure 1. Mean and standard error of the mean (SEM) of the parathyroid hormone (PTH) 25-OHD<sub>3</sub>, 1,25 (OH)<sub>2</sub>D<sub>3</sub> and serum calcium (Ca) prior, during, and 4 weeks after calcitriol treatment in patients with psoriasis.



calcitriol therapy and 30 days after treatment was discontinued. There was no significant difference among these values. There was no correlation between the concentration of  $1,25(\text{OH})_2\text{D}_3$  and the clinical improvement of the patients.

Two patients developed increased urinary calcium levels at the last follow-up visit which was explained on the basis of poor compliance with their low calcium diets.

Table II

	Ca	P	AP	PTH	1, 25 (OH) $_2$ D	25 OHD
n	10	10	8*	10	10	5
x	9.6	3.5	92	31.8	30.4	30.3
SD	0.5	0.6	14.5	11.5	9.6	9.6
SE	0.2	0.2	5.5	3.8	3.2	3.8

Normal Values: Ca: 8.5-10.5 mg/dL; P: 2.5-4.5 mg/dL;  
AP: 35-115 U/L; PTH: 10-65 pg/mL; 1, 25 (OH) $_2$  D  
18-74 pg/mL; 25 OHD: 15-112 ug/ml

\*Two patients that showed high values were excluded

### Discussion

Three important conclusions can be derived from this study. First, calcitriol at 0.5 mc given daily at bedtime for 3 months is not effective in the treatment of psoriasis. Although 40% of our patients showed some type of improvement, it was moderate and none had total clearing of their psoriasis. Some decrease in scaliness and thinning of plaques were noticed, changes that have been reported in previous studies.<sup>7, 12</sup> (Figure 2A- 2B).



Figure 2. Psoriatic plaque in the elbow of patient #2 before (2a) and 6 weeks after treatment with calcitriol 0.5 mcg daily (2b).

Second, side effects to the drug at this dose were not observed. The convenience of one single administration at bedtime helped to increase the compliance in our patients.

Third, any effect that calcitriol may have in psoriasis cannot be explained on the basis of the vitamin D effects on calcium metabolism since all Vitamin D metabolites were within normal limits before, during and after the trial.

Mac Laughlin et al<sup>4</sup> in 1985 reported that cultured psoriatic fibroblasts had a partial resistance to the differentiating activity of  $1,25(\text{OH})_2\text{D}_3$ . He predicted that cultured psoriatic keratinocytes also would have a partial resistance. This finding prompted several clinical studies using oral or topical administration of Vitamin D metabolites in the treatment of psoriasis.

In 1986, Morimoto et al<sup>5</sup> reported five cases of psoriasis treated with daily topical calcitriol in a petrolatum base. He used concentrations of 0.1 mc/g or 0.5 mc/g and found curative effects on the plaques treated. He did not find any side effects or significant difference in mean serum values of Vitamin D metabolites. He did note one of his patients to have decreased circulating levels of  $1,25(\text{OH})_2\text{D}_3$  and attributed this finding to the aggravation of the psoriasis during the trial.

In the same year, Morimoto et al<sup>6</sup> reported another study in which they treated 40 patients with psoriasis in three different ways. Seventeen patients received  $1,25(\text{OH})_2\text{D}_3$  orally 1.0 ug/day for six months; five patients received  $1,25(\text{OH})_2\text{D}_3$  0.5 ug/day orally for six months and nineteen patients received  $1,25(\text{OH})_2\text{D}_3$  topically at a concentration of 0.5 ug/g for eight weeks. They found improvement in 76% of patients in Group I; 25% of patients in Group II and 84% of patients in Group III. Group II of this report showed similar results to our study. Although the drug was given for six months, the only patient that responded showed improvement three months after the start of treatment. Although both populations are small, they found that 25% of their patients improved, compared to 40% of patients in our study.

These investigators found significant increases in serum calcium levels in patients treated with the oral preparations. These changes did not occur in our patients when treated with a daily dose of 0.5 ug of calcitriol.

More recently, Smith, Pincus and Holick<sup>7</sup> published a very complete study demonstrating the effect of oral or topical calcitriol on cultured fibroblasts and keratinocytes of psoriatic patients. In their clinical trial they treated 14 patients with oral calcitriol starting at doses of 0.25 ug/day and increasing the dose up to 2.0 ug/day as tolerated. They also treated three patients with topical calcitriol at a concentration of 3 ug/g in petrolatum.

They found significant clearing of plaques in 10 of the 14 patients treated orally and in all three of the patients treated topically.

It is important to note that probably, the dosage of oral calcitriol needs to be individualized as patients responded variably to the same dosage of the drug.

Smith et al<sup>7</sup> also found that most improvement is seen when using doses of calcitriol above 1.0 ug/day. In our

study, a dosage of 0.5 ug/day was not effective.

Morimoto and Yoshikawa<sup>8</sup> reviewed their experience with calcitriol and reported an analytical study of their previously reported clinical trial.<sup>6</sup> They found significant elevations of serum calcium levels after three months of treatment with oral calcitriol and a negative correlation between serum level of 1, alpha-25 (OH)<sub>2</sub> D<sub>3</sub> and the area of severity of psoriasis in the patient. We did not find these correlations in our study.

More recently, Kragfalle<sup>13</sup> reported a study using topical application of a synthetic cholecalciferol analogue named calcipotriol. He treated 50 patients with psoriasis and found improvement in 63% of them when using a 50 ug/g concentration ointment. He stated that calcipotriol is 100 times less potent in its effects on calcium metabolism and noted that there were no changes in calcium levels during the study. Interestingly, he reported an increased incidence of facial dermatitis which had not been described previously with 1, alpha-25 (OH)<sub>2</sub> D<sub>3</sub>.

In summary, this study demonstrates that calcitriol in a daily dose of 0.5 ug is not significantly effective as a single treatment in moderate to severe psoriasis. Further studies with calcitriol as an adjuvant therapy to topical steroids or photochemotherapy are necessary. Topical preparations of Vitamin D analogues may also be important in the future of this novel therapeutic alternative for psoriasis.

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# Melanoma Maligno en Puerto Rico

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**Resumen:** Se efectuó un estudio epidemiológico de melanoma maligno mediante la revisión de todos los casos de melanomas reportados al Registro de Cáncer de Puerto Rico entre los años 1981 al 1987. Se documentaron un total de 367 casos nuevos con una incidencia anual que fluctuó entre 1.20 y 2.12 por 100,000 habitantes y un promedio de 1.59.

La mayoría de los pacientes tenían entre los 40 y 80 años de edad, con una mayoría en los 60. Casi la mitad de los tumores ocurrieron en las extremidades, sobre todo en los pies, compartiendo esta tendencia con otras razas como los negros y japoneses. El tipo clínico-histológico más frecuente lo fue el melanoma superficial expansivo seguido del acral lentiginoso, el nodular y el melanoma lentigo maligna. Cerca de un tercio del total de casos no fue clasificado de acuerdo al tipo histológico, mientras que los niveles de Clark y el grosor de Breslow no fueron reportados en 44 y 84% de los casos respectivamente.

Cuando comparamos nuestra data a la de un estudio previo en Puerto Rico entre los años de 1977 al 1980, la incidencia anual promedio de casos nuevos aumentó de 0.92 a 1.59 por 100,000 habitantes, documentándose un aumento de incidencia en nuestra población, pero no tan significativo como el aumento registrado en los Estados Unidos.

La incidencia de melanoma maligno continua aumentando a un ritmo alarmante a nivel mundial durante las últimas décadas, particularmente entre caucásicos.<sup>1-5</sup> En los Estados Unidos se ha registrado un aumento de 6 veces la incidencia anual durante los últimos 50 años.<sup>5</sup> En algunas partes del suroeste y sureste de los Estados Unidos, la incidencia entre caucásicos es más de 30 por 100,000 individuos, similar a la del cáncer de colon.<sup>6</sup>

El pronóstico de pacientes con melanoma depende de una serie de factores que incluyen el tipo clínico histológico, nivel de invasión (Clark), grosor del tumor (Breslow), localización anatómica y la presencia o ausencia de ulceración.<sup>7</sup> Se considera que todos los parámetros se deben de establecer en cada caso para poder determinar el tratamiento óptimo de cada paciente y poder determinar con mayor exactitud la sobrevida de los casos de melanoma en la población. De todos estos, la medida del grosor del tumor de Breslow se considera el factor más importante en cuanto a pronóstico.<sup>8</sup>

Es el propósito de este estudio determinar las características epidemiológicas, clínicas e histológicas de los

casos de melanoma maligno en Puerto Rico desde 1981 al 1987, y comparar nuestros hallazgos con estudios previos llevados a cabo en Puerto Rico, Estados Unidos y en poblaciones hispanas en los Estados Unidos.

## Materiales y Métodos

Se revisaron los casos de melanoma maligno reportados al Registro de Cáncer de Puerto Rico desde el 1981 al 1987. En cada caso se determinó la edad, sexo, localización anatómica, descripción clínica, reporte histopatológico incluyendo el diagnóstico en cuanto a tipo clínico histológico de melanoma, nivel de Clark, grosor de Breslow y el tiempo de sobrevida de cada paciente.

## Resultados

Un total de 367 casos fueron reportados en los siete años incluidos en el período estudiado (Tabla 1). De estos, 49.3% eran mujeres y 50.7% eran hombres. Las edades de los pacientes fluctuaban entre los 22 meses a los 106 años. La edad promedio era de 58.9.

Tabla 1

AÑO	NUMERO DE CASOS	CASOS POR 100,000 HAB.
1981	39	1.20
1982	42	1.28
1983	56	1.71
1984	47	1.44
1985	63	1.92
1986	50	1.52
1987	70	2.12

TOTAL 367

La incidencia anual por cada 100,000 habitantes, desde el 1981 al 1987 fluctuó entre 1.20 a 2.12, con una incidencia anual promedio de 1.59 (Tabla 2). Aproximadamente una tercera parte del total de pacientes había muerto al momento de revisar la data.

La mayor parte de los pacientes se encontraba entre las edades de los 40 a los 80 años de edad, con un pico entre los 60 a los 69 años (Tabla 3). En la mayor parte de los casos (48.5%), el tumor se encontraba localizado en las extremidades y preferiblemente en el área de los pies. Otras áreas más frecuentes lo eran el torso, la cabeza y el cuello (Tabla 4).

Es notable que en mujeres había un mayor número de casos localizados al área de los brazos y piernas excluyendo las áreas acrales. En hombres se encontró un mayor número de casos localizados al área de la espalda, la cabeza y el cuello (Tabla 5).

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Tabla 2

## INCIDENCIA POR 100,000 HAB.

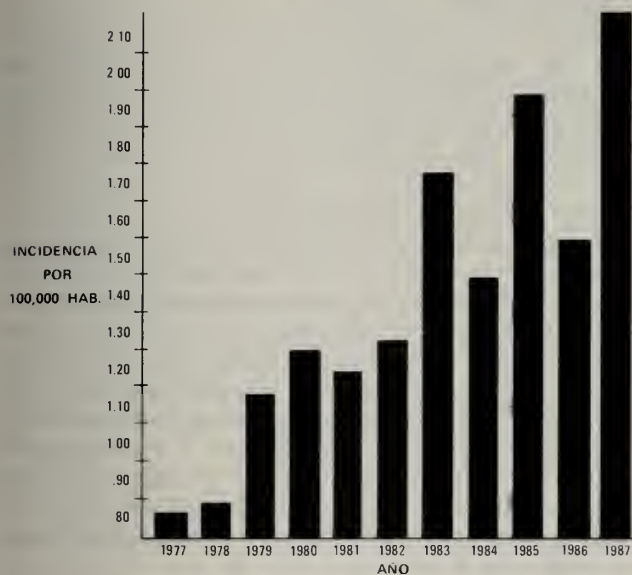


Tabla 3

Edad	Total de Casos	Por ciento (%)
0-9	1	0.2
10-19	6	1.6
20-29	17	4.6
30-39	41	11.2
40-49	48	13.1
50-59	48	13.1
60-69	78	21.3
70-79	72	19.6
80-89	43	11.7
90-99	11	3.0
100-109	1	0.2

Tabla 4

## Distribución Anatómica

Localización	Número de Casos	Por ciento (%)
Cabeza y Cuello	56	15.2
Brazo y Antebrazo	53	14.4
Muslo y Pierna	37	10.08
Manos	7	1.9
Pies	81	22.07
(Total en extremidades)	178	48.5
Pecho	22	5.9
Espalda	56	15.25
Abdomen	4	1.08
Nalgas	5	1.36
Torso - (Sin especificar)	4	1.0
(Total en el torso)	91	24
Desconocido	43	11.71

Tabla 5

## Distribución Anatómica por Sexo

	Mujeres (160)	Hombres (165)
Cabeza y Cuello	15% (24)	20.6% (34)
Brazos	18.7% (30)	10.3% (17)
Piernas	18.7% (30)	6.6% (11)
Manos	2.5% (4)	1.8% (3)
Pies	20% (32)	28.4% (47)
(Extremidades)	60% (96)	47.2% (78)
Pecho	7.5% (12)	5.4% (9)
Espalda	13.7% (22)	23.6% (39)
Abdomen	1.2% (2)	1.2% (2)
Nalgas	2.5% (4)	1.2% (2)
Torso	0% (0)	0.6% (1)

Total 325

El tipo histopatológico más común lo fue el superficial expansivo, seguido del acral lentiginoso, el nodular, y por último el lentigo maligna melanoma (Tabla 6). Un tercio del total (29.7%) de melanomas no había sido clasificados en los distintos tipos histopatológicos. Se reportaron los niveles de Clark en un 56% y el grosor de Breslow en solamente los 16% de los casos. En un 3% se reportó la presencia histológica de un nevo asociado.

Al correlacionar el tipo histopatológico de melanoma con el grosor de Breslow tenemos que los melanomas de tipo acral lentiginoso y nodular eran más profundos y usualmente medían más de 1.5mm, a diferencia del superficial expansivo y el lentigo maligna melanoma que tendían a presentar un grosor menor de 1.49mm (Tabla 7). Al correlacionar la localización anatómica de la lesión con el grosor observamos que los melanomas localizados en el área de las extremidades inferiores, pies y torso medían más de 1.5mm en grosor, a diferencia de melanomas localizados en las extremidades superiores, cabeza y cuello que eran más superficiales (Tabla 8).

Aproximadamente una cuarta parte de los tumores había metastatizado al momento de revisar la data, y aproximadamente un 3% de los pacientes tenía otro tipo de cáncer asociado.

Tabla 6

## Clasificación Histopatológica

Diagnóstico Patológico	Número de Casos	Por ciento (%)
Superficial Expansivo	78	21.2
Acral Lentiginoso	73	20.0
Nodular	52	14.0
Lentigo Maligna	30	8.17
No Clasificado	109	29.7
Desconocido	26	7.08
(Metastático)		
Niveles de Clark	56.13%	
Grosor de Breslow	16.3%	
Presencia Histológica		
De un nevo	3.0%	

Tabla 7

Tipo de Melanoma	GROSOR (MM)			
	≤0.75	0.76-1.49	1.50-2.99	≥ 3.0
Superficial expansivo (18)	44% (8)	22% (4)	22% (4)	11% (2)
Acral lentiginoso (13)	0	15% (2)	46% (6)	38% (5)
Nodular (17)	11% (2)	18% (3)	35% (6)	35% (6)
Lentigo maligna (7)	42% (3)	28% (2)	14% (1)	14% (1)
Desconocido (14)	21% (3)	14% (2)	28% (4)	36% (5)
Total (69)	18.8%			

Tabla 8

Localización de la Lesión	GROSOR (MM)			
	≤0.75	0.76-1.49	1.50-2.99	≥ 3.00
Cabeza y Cuello (13)	46% (6)	15% (2)	23% (3)	15% (2)
Torso (14)	21% (3)	14% (2)	36% (5)	28.5% (4)
Brazo y Antebrazo (13)	46.1% (6)	38.4% (5)	0 (0)	15.3% (2)
Muslo y Pierna (10)	0 (0)	10% (1)	50% (5)	40% (4)
Manos (2)	0 (0)	50% (1)	0 (0)	50% (1)
Pies (13)	0 (0)	7.6% (1)	54% (7)	38.4% (5)
Nalgas (1)	0 (0)	0 (0)	0 (0)	100% (1)

Total 66 (17.9%)

### Discusión

Al comparar nuestra data que corresponde a los años de 1981 a 1987 con el estudio previo en Puerto Rico llevado a cabo desde el 1977 al 1980,<sup>9</sup> vemos que el número promedio de casos por año en el período comprendido entre el 1977 al 1980 lo fue de 31.7 lo que contrasta con el estudio actual donde fue de 52.4 casos. La incidencia anual promedio por cada 100,000 habitantes fue de .92 en el período entre 1977 al 1980 mientras que del 1981 al 1987 fue de 1.59. El área anatómica más comunmente afectada en ambos estudios fue las extremidades y específicamente el área de los pies, seguido del torso y por último el área de la cabeza y el cuello.

El tipo histológico más común en el estudio anterior lo fue el superficial expansivo seguido por el melanoma nodular, el acral lentiginoso y el lentigo maligna melanoma. En el estudio actual el más común lo fue el superficial expansivo seguido por el acral lentiginoso, el nodular y el lentigo maligna melanoma. Es importante recalcar que en el estudio anterior, aproximadamente la mitad de los casos no habían sido clasificados en cuanto a tipo clínico-histológico mientras que en el presente estudio no se había hecho en aproximadamente una tercera parte de los casos.

Si combinamos la data de ambos estudios vemos un total de 494 casos entre el 1977 al 1987 (Tabla 2). La distribución por sexo fue equivalente, a razón aproximada de uno a uno. La incidencia por 100,000 habitantes entre 1977 al 1987 subió de .82 en 1977 a 2.12 en 1987. El área más comunmente afectada fue las extremidades, específicamente el área de los pies. Otras áreas comunmente afectadas lo fueron el torso y el área de cuello y cabeza. El tipo de melanoma más común lo fue el superficial expansivo seguido del acral lentiginoso, el nodular y por último el lentigo maligna melanoma.

Aproximadamente un 35% de los casos no habían sido clasificados histológicamente; los niveles de Clark se reportaron en 54% de los casos y el grosor de Breslow en solamente 14%.

Si comparamos nuestra data con el estudio de Kopf<sup>10</sup> de 719 casos realizado en Nueva York en pacientes caucásicos entre 1977 al 1982, tenemos que la distribución por sexo en ambos estudios es similar, y el área anatómica más frecuentemente afectada lo fue el área de las extremidades. En nuestro estudio encontramos un mayor número de casos localizados en el área del pie a diferencia al de Kopf<sup>10</sup> en que eran principalmente, en el área de brazos y piernas incluyendo las áreas acrales. En el estudio de Kopf se encontró un mayor número de casos en el área del torso. El tipo histopatológico de melanoma más común en ambos estudios lo fue el superficial expansivo aunque había una gran diferencia, ya que Kopf<sup>10</sup> reportó cerca del 82% de los melanomas como superficial expansivo comparado con 20% en el estudio actual. También es importante el hecho de que en nuestro estudio el segundo tipo de melanoma más común lo fue el acral lentiginoso y no el melanoma de tipo nodular como en el estudio de Kopf.

Black<sup>11</sup> comparó la incidencia de melanoma entre la población de blancos e hispanos residentes en el estado de Nuevo México entre los años de 1979 a 1986. Al comparar nuestra data con el estudio de Black vemos que la incidencia por cada 100,000 habitantes fue mucho más alta en los pacientes caucásicos de Nuevo México con 16, al compararlo con 2 para los hispanos de Nuevo México y 1.39 para los puertorriqueños en nuestro estudio. El área más comunmente afectada en las tres poblaciones lo fueron las extremidades, pero en pacientes puertorriqueños y en los hispanos de Nuevo México se encontró un mayor número de casos localizados en las áreas acrales mientras que en los caucásicos la mayoría de casos fue en el área de brazos y piernas excluyendo las áreas acrales. Estudios previos han demostrado que la incidencia del melanoma acral lentiginoso varía de acuerdo a la raza.<sup>12-14</sup> Los negros tienen la incidencia más alta con 66 a 70% del total de casos mientras que en los japoneses ocurren en el 49% y en los caucásicos de 2 a 13% del total. Al combinar la data del presente estudio con el anterior, cerca de un cuarto (25%) del total de melanomas en puertorriqueños ocurren en áreas acrales siendo en su mayoría del tipo acral lentiginoso.<sup>9</sup> También en pacientes caucásicos de Nuevo México se encontró un mayor número de melanomas localizados al área del torso al compararlo con los hispanos de Nuevo México y los puertorriqueños. El tipo histopatológico de melanoma más común en estas tres poblaciones lo fue el superficial expansivo. En pacientes hispanos y caucásicos de Nuevo México<sup>11</sup> los números eran sustancialmente mayores con 61% y 78% respectivamente, comparado con solamente 20% para Puerto Rico. El segundo tipo de melanoma más común en pacientes puertorriqueños e hispanos de Nuevo México lo fue el acral lentiginoso, a diferencia de pacientes caucásicos de Nuevo México en que lo fue el de tipo nodular.

Vemos pues que la incidencia por cada 100,000 habitantes en Puerto Rico es comparable a la de pacientes hispanos de Nuevo México en los Estados Unidos y



significativamente menor a la de pacientes de origen caucásico. En Puerto Rico se ha registrado un aumento en la incidencia de melanoma, pero no tan marcado como el aumento registrado en caucásicos en los Estados Unidos.<sup>5-6</sup>

La incidencia en Puerto Rico es igual en hombres y mujeres con una cuarta parte del total de casos localizados en áreas acrales como las palmas y plantas (25%). En mujeres existe un mayor número de casos localizados al área de brazos y piernas, mientras que en hombres hay un mayor número localizados en las áreas de pies y espalda. En ambos sexos la mayor parte de los casos fue en las extremidades.

Un hallazgo muy significativo en este estudio constituye el hecho de que en Puerto Rico hay un gran número de casos en el que el reporte patológico no incluye los niveles de Clark (44%) ni la profundidad de invasión de Breslow (84%), factores que son cruciales para propósitos de pronóstico y manejo en pacientes con melanoma maligno.

El aumento en la incidencia de melanoma junto con la disminución en la morbilidad y mortalidad asociada al diagnóstico y tratamiento temprano del tumor ofrecen apoyo al aumento en entusiasmo tanto del público en general como de la profesión médica en la educación dirigida al diagnóstico temprano de esta condición.

**Summary:** An epidemiological study of malignant melanoma in Puerto Rico was done by reviewing the Puerto Rico Cancer Registry for all melanoma cases reported between the years 1981 to 1987. A total of 367 new cases were documented with the annual incidence ranging from 1.20 to 2.12 per 100,000 inhabitants with a mean of 1.59.

Most of the patients were between 40 and 80 years of age with a peak in the sixties. Nearly one half of the tumors were located on the extremities, most notably on the feet, sharing this predilection with Blacks and Japanese. The most frequently recognized clinicohistologic type was the superficial spreading melanoma followed by the acral lentiginous, the nodular and the lentigo maligna melanoma. Nearly one third of the total cases were not classified according to the histologic type, while Clark's levels and Breslow's thickness were not reported in 44 and 84% of the cases, respectively.

When compared to a previous study during 1977 to 1980, the average annual incidence of new cases increased from 0.92 to 1.59 per 100,000 documenting an increased incidence of the condition in our population, but not as significant as that registered in the United States.

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# Bullous Pemphigoid and Malignancy

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**Summary:** Bullous pemphigoid has been reported in multiple publications to be associated with malignant neoplasms of different internal organ systems. This relationship was studied among forty patients seen at the Dermatology Clinics of the Puerto Rico Medical Center.

The study demonstrated that Puerto Rican patients with bullous pemphigoid do not show an increased incidence of internal malignancy when compared with the general population matched for age, sex and study period. We conclude that extensive diagnostic studies for malignant neoplasms should not be the standard of care in patients with bullous pemphigoid. Additional studies should be guided by the clinical history and physical findings.

Since the turn of the century, the relationship between bullous pemphigoid and malignancy has been a highly controversial topic. In 1909, Bogrow<sup>1</sup> reported a 28-year-old Russian woman who developed a vesiculo-bullous eruption two months before the development of a carcinoma of the labium. The eruption cleared within three days after surgical treatment of the carcinoma. Since then, several reports in the literature have tried to establish a temporal relationship of bullous pemphigoid with malignancy.

Bullous pemphigoid has been reported to be associated with malignant neoplasms of the urinary tract,<sup>2,3</sup> lung,<sup>4,5</sup> ovary,<sup>6</sup> breast,<sup>3</sup> pancreas,<sup>7</sup> gastrointestinal tract,<sup>8</sup> skin<sup>9</sup> and the lymphoreticular system.<sup>10</sup> In spite of these multiple reports, many authors feel that the increased incidence of malignancy in patients with bullous pemphigoid is not statistically significant, but rather coincidental.

The purpose of this study was to determine the incidence of malignancy in those patients with bullous pemphigoid seen at the Puerto Rico Medical Center, and compare it with the incidence of malignancy in the general Puerto Rican population matched for sex, age and study period.

## Materials and Methods

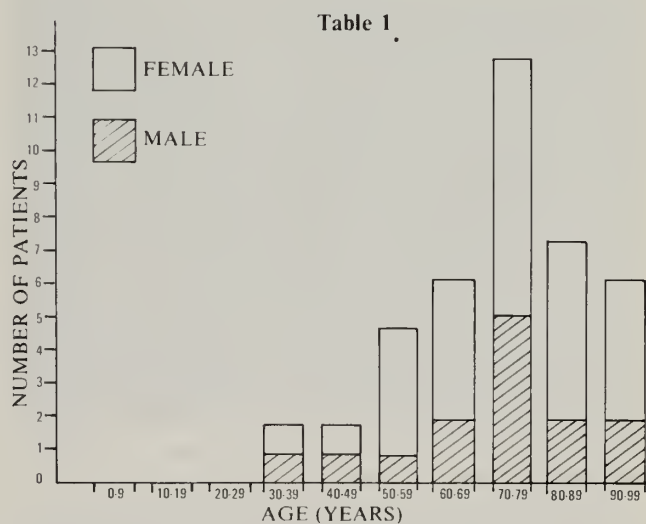
Forty patients seen in our institution with the clinical and histopathological diagnosis of bullous pemphigoid during the period between 1977 and 1987 were included in our study. The records were reviewed for age, associated medical conditions, type of systemic malignancy and clinical course.

## Results

Out of forty patients with bullous pemphigoid which were evaluated, there were 13 men (32%) and 27 women (68%) with a median age of 72 and a mean age of 71.3 years (Table 1). The follow-up period ranged from one to fifteen years with sixty-five percent of the cases having more than three years of follow-up.

Malignant neoplasms were found in three out of the 40 (7.5%) patients. The neoplasms included one case of classical Kaposi's sarcoma, one patient with an ovarian tumor and another with carcinoma of the breast. In none of these three cases, the course of the skin disease followed or predicted the course of the malignancy.

Using epidemiological data from the Department of Health of Puerto Rico the mean incidence of cancer in the general population was calculated for the period between 1977 and 1987 based on the age and sex of the patients of the study (Table 2).



DISTRIBUTION OF PATIENTS WITH BULLOUS PEMPHIGOID BY AGE AND SEX AT TIME OF DIAGNOSIS

Table 2

## Epidemiological Data

- MEAN POPULATION OF 30 TO 99 YEARS BETWEEN 1977 - 1987 = 1,500,000
- NUMBER OF MALIGNANCY CASES REGISTERED BETWEEN 1977 - 1987 FOR AGE 30 TO 99 = 60,000

The expected incidence of malignancy in the group of patients was approximately 4% as compared with the 7% incidence found in our cases. Compared with the expectancy of cancer in the Puerto Rican population in a corresponding age and sex group, the results of the chi-square analysis showed no significant difference ( $P < .05$ ) between the incidence of malignant disease in the bullous pemphigoid group and the general population.

### Discussion

The first epidemiological report regarding bullous pemphigoid and malignancy was that of Lim et al<sup>11</sup> from St. John's Hospital where they studied 103 patients with bullous pemphigoid and found 12 cases with an associated internal malignancy (11% of the total).

In 1973, Paslin<sup>12</sup> reviewed the cases at the University of Pennsylvania from 1960 to 1972 and only one patient out of 19 cases presented with a systemic malignancy.

Stone and Schroeter,<sup>2</sup> evaluated the data from 73 patients with bullous pemphigoid seen of the Mayo Clinic between 1960 and 1972 and compared it with data from 146 controls (73 patients with psoriasis and 73 patients with contact dermatitis) matched for age, sex, and calendar year of diagnosis. In the three groups, eight patients with bullous pemphigoid, 11 with contact dermatitis, and ten with psoriasis were found to have malignant disease within the period covering the five years before and five years after the diagnosis of the skin disease. They concluded that there was no significant difference between the three groups regarding the incidence of internal malignancy.

In 1977, Amhed, Maize and Provost,<sup>13</sup> reported only one case of malignancy out of 33 bullous pemphigoid patients (3%). In 1978, Chorzelski et al,<sup>5</sup> reviewed 110 cases of bullous pemphigoid diagnosed in Poland between 1968 and 1979 and found that 12 (11%) of them had an associated internal malignancy. They compared this data with the mean incidence of cancer in the population of Poland and found a statistically significant increased incidence of malignancy in the patients with bullous pemphigoid.

Retrospective studies have several limitations, such as difficulty in establishing an ideal control group and the fact that limited information is obtained from the medical records. These limitations have to be considered when adequate statistical analysis are performed. Our study showed that our group of patients with bullous pemphigoid do not have an increased incidence of internal malignancy when compared with the general population matched for age, sex and study period. We conclude that extensive diagnostic studies for malignant neoplasms should not be the standard of care in patients with bullous pemphigoid. The clinical history and physical findings should be used to determine any necessary additional studies.

**Resumen:** Se estudia la asociación entre penfigoide ampolloso y neoplasias malignas de diversos órganos internos en 40 pacientes vistos en las Clínicas de Dermatología en el Centro Médico de Puerto Rico.

Cuando se comparan estos pacientes con la población general en cuanto a edad, sexo y período de estudio, se encontró que no tenían una incidencia mayor de malignidad interna. Se concluye que estudios extensos para diagnosticar neoplasias internas no debe ser la regla general en la evaluación de pacientes con penfigoide ampolloso. El historial clínico y el examen físico deben ser las guías para estudios adicionales.

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# Acral PUVA - Induced Pigmented Macules

Alma Cruz, MD  
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**Abstract:** This report describes four patients with chronic psoriasiform dermatitis of the palms and soles who developed pigmented macular lesions after localized photochemotherapy (PUVA) to these areas. These lesions had varied histopathologic presentations including lentigines, atypical melanocytic proliferation and a junction nevus suggesting a wide clinico pathologic spectrum in the PUVA-induced pigmented macules.

Oral methoxalen photochemotherapy (PUVA) for the treatment of psoriasis has been associated with hyperpigmented macular lesions at irradiated areas, especially in fair-skinned individuals.<sup>1, 2</sup> Freckles, lentigines, melanocytic nevi and occasionally cytologically atypical melanocytic proliferation have been described.<sup>3, 4, 5, 6</sup>

Localized photochemotherapy is a variation of this modality of treatment in which selected regions of the skin are irradiated, especially in patients with palmo-plantar psoriasis and other recalcitrant conditions like chronic nummular and dyshidrotic dermatitis. This is a report of four patients who developed hyperpigmented macular lesions on acral surfaces after localized chemotherapy.

## Case Reports

**Case 1.** A 50-year-old male patient without history of systemic illness but with a 30-years history of recurrent erythematous scaly dermatitis on the palms and soles was seen at our clinics in 1984 with a diagnosis of psoriasis which was confirmed by a skin biopsy. PUVA therapy to the palms and soles was started with a fair response to treatment after a total dose of 762 joules /cm.<sup>2</sup> Three months after finishing the therapy, the patient noticed a 4mm hyperpigmented macule on the flexural aspect of the middle finger of the left hand (Fig. 1). An excisional biopsy was performed.

Histopathological examination revealed hyperkeratosis and focal parakeratosis of the stratum corneum. There was epidermal psoriasiform hyperplasia with marked hyperpigmentation of the basal layer in which there was an increased number of hypertrophic melanocytes with prominent arborizing dendrites (Fig. 2). Collections of mononuclear cells were seen in the papillary dermis.

**Case 2.** A 64-year-old healthy female patient was seen with a six-year history of recurrent palmo-plantar erythema and vesiculation diagnosed as chronic dyshidrosis. In 1983 PUVA therapy was started receiving 57 treatments for a total dose of 954.4 j/cm<sup>2</sup>.



Figure 1.

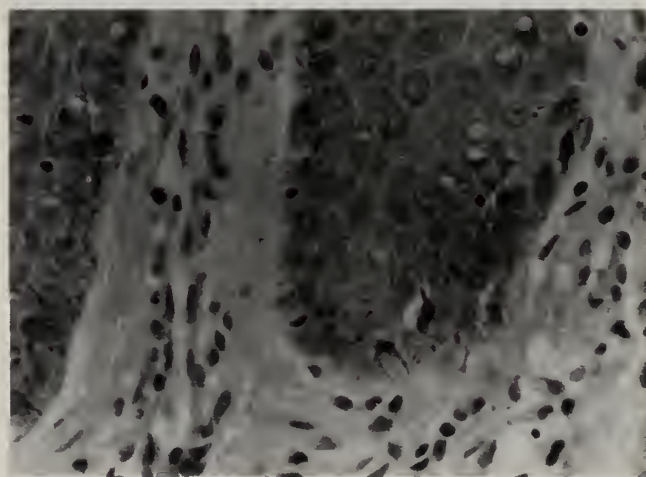
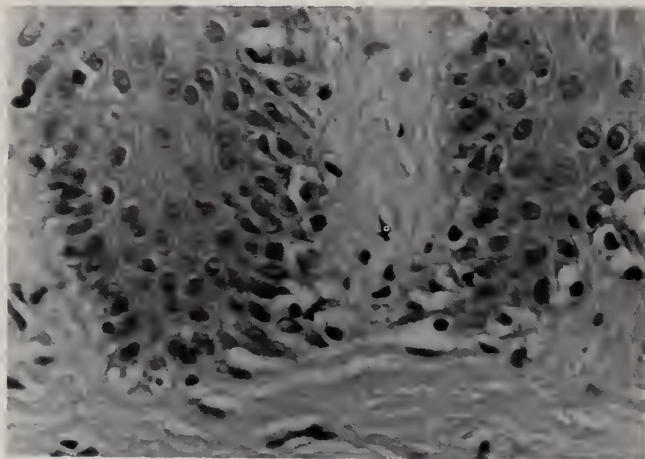


Figure 2.

One year after her last treatment, in a follow-up visit, several scattered 2mm, light-brown macules were noticed on the right sole. She referred that these lesions were not present before PUVA treatment, but could not specify their time of appearance.

Punch biopsy of one of the lesions revealed scattered, large dendritic melanocytes on the basal layer accompanied by hyperpigmentation (Fig. 3).

**Case 3.** A 28-year-old woman was evaluated in 1981 at the Dermatology Clinic where a diagnosis of palmo-plantar psoriasis was made. Due to unresponsiveness to conventional treatment, localized photochemotherapy was started receiving 72 treatments for a total dose of 1016 j/cm<sup>2</sup> in a span of 2 1/2 years.



Figure

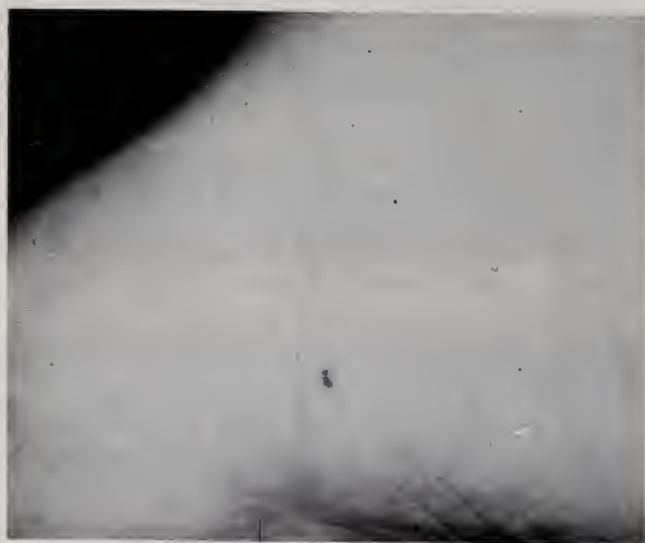


Figure 4.

There was good response to therapy with complete resolution of lesions.

Eight months after the last PUVA treatment, she noticed a 3mm brown macule with well-defined borders on the right sole (Fig. 4). Histologic examination of the lesion revealed horizontally-arranged nests of melanocytes at the dermo-epidermal junction with few scattered melanophages at the papillary dermis. A perivascular infiltrate of mononuclear cells and papillary fibroplasia were also present. The lesion was diagnosed as a junctional nevus (Fig. 5)

**Case 4.** A 71-year-old hypertensive female patient well-controlled with diuretics, with diagnosis of psoriasis localized on the palms since 1983, was started on localized PUVA in 1984 receiving 31 treatments for a total dose of 540 j/cm<sup>2</sup> with complete resolution of lesions.

Three months after finishing the therapy, the patient noticed multiple light brown, 1-3mm macules on the previously exposed areas.

Punch biopsy revealed increased number of melanocytes at the dermoepidermal junction with hyperpigmentation of the basal layer.

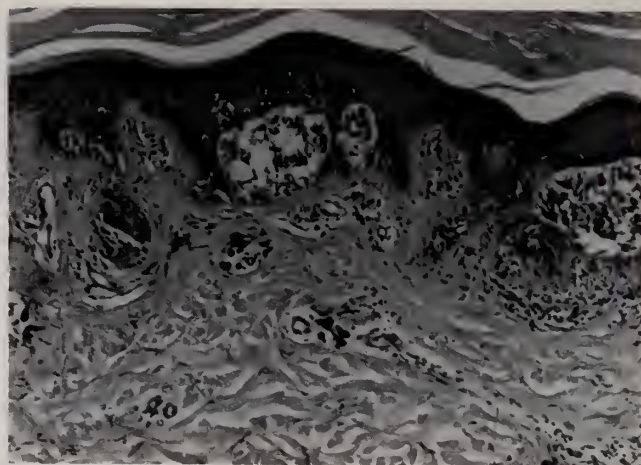


Figure 5.

### Discussion

Macular pigmented lesions in individuals undergoing PUVA for psoriasis or other chronic skin disorders have been called by different names, namely, star-like hyperpigmented lentigines,<sup>4</sup> freckles,<sup>1</sup> stellate hyperpigmented freckles,<sup>2</sup> nevus spilus-like hyperpigmentation<sup>3</sup> and hyperpigmented spots.<sup>5</sup> Microscopic evaluation of these lesions has revealed a wide variety of histologic findings.

Konrad, Gschnait and Wolff<sup>4</sup> reported poikiloderma-like pigmentary changes after repeated PUVA overdose in which large, numerous active but not atypical melanocytes were the major findings. Large, dendritic melanocytes containing many melanosomes in various stages of development were described by Bleeher<sup>1</sup> in three patients that developed PUVA-induced stellate freckles.

Zaynoun et al<sup>7</sup> confirmed the stimulatory effect of PUVA over melanocytes but reported the absence of changes in size or distribution pattern of melanosomes. However, Hashimoto et al<sup>8</sup> described double-nucleated and clusters of melanocytes with alteration of distribution, size and arrangement of melanosomes in keratinocytes.

Electron microscopic studies performed by Zelickson<sup>9</sup> demonstrated the presence of an increased number and size of melanocytes, disruption of intracytoplasmic organelles (abnormal distorted endoplasmic reticulum and large lysosomes), clusters of melanocytes in the lower part of the epidermis and free affected melanocytes in the dermis. These abnormal melanocytes were present up to 15 months after PUVA therapy.

Degenerative changes of melanocytes and disruption of the basal lamina was also described by Szekeres.<sup>5</sup> Gschnait et al<sup>10</sup> found increased number of strongly DOPA-positive and highly dendritic melanocytes in mottled skin induced by PUVA. Rhodes, Harist and Momtaz-T<sup>6</sup> studied eleven PUVA-induced pigmented macules and demonstrated that they were characterized by a lentiginous proliferation of large melanocytes, which in some cases, might be slightly atypical and suggested continual monitoring of these lesions.

There have been a least three reported cases of



malignant melanoma in patients treated with this therapeutic modality. Forrest and Forrest<sup>11</sup> reported a malignant melanoma arising during photochemotherapy for vitiligo, and Marx et al<sup>12</sup> described two patients who were treated with PUVA for psoriasis and developed cutaneous lesions of malignant melanoma in situ. In 1984, Johnsen reported a 22 year-old female patient who had received PUVA to the palms for palmo-plantar pustulosis and who later developed a superficial spreading malignant melanoma on the right palm and two months later developed a junctional nevus on the left palm.

We are reporting four cases of macular pigmented lesions on acral areas arising during localized PUVA therapy. The spectrum of the lesions ranged from simple freckles to lentigines with occasional atypical melanocytes and a junction nevus. It should be pointed out that acral malignant melanoma is characterized in its early stage by large, dendritic and atypical melanocytes in the lower epidermis<sup>14</sup> like those described in the PUVA pigmented lesion as presented by our first patient. It can be concluded from these four patients and the experience of other investigators that the clinicopathologic spectrum of PUVA-induced lesions may vary from simple freckles, lentigines, atypical melanocytic proliferations to malignant melanoma.

Which individuals are predisposed to these lesions? What frequency, duration and intensity of the treatment are required for the induction of these lesions? These are questions that need to be answered. Because of the absence of information about the incidence and prevalence of these lesions, close follow-up of patients and adequate reporting is needed until the long-term safety of this treatment is established, especially in our population in whom malignant melanoma is frequently located in acral regions.<sup>15</sup>

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# Clinicopathologic Study on Pityriasis Alba

Rafael F. Martín, MD  
Aida Lugo-Somolinos, MD  
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**Summary:** Pityriasis alba (PA) is a relatively common skin disorder usually seen in children and young adults characterized by the presence of superficial hypopigmented macules. A clinicopathologic study on pityriasis alba was undertaken which showed an increased occurrence of the disease in preadolescent children with an equal incidence in boys and girls, and a predominance of white over black patients. There was an increased personal history of atopy and the skin lesions were found to occur most frequently in the arms and face followed by the legs and the trunk.

Histologic evaluation of biopsy specimens of PA showed consistent spongiosis, follicular spongiosis, focal parakeratosis and acanthosis in the epidermis together with a superficial perivascular lymphocytic infiltrate.

Pityriasis alba (PA) is a relatively common skin disorder usually seen in children and young adults characterized by the presence of superficial hypopigmented macules with slight overlying scaliness and a slightly elevated erythematous border. Individual lesions can measure from 0.5 to 5 cms in diameter and are usually located on the face, neck, shoulders and the extensor surface of the arms (Fig. 1). They are mostly asymptomatic although some patients may complain of mild pruritus. Boys are equally affected as girls. Although these skin lesions are more prominent in dark-skinned individuals, an increased incidence of PA in black patients over white patients has been debated.<sup>1,2</sup> A seasonal variation has been observed, with exacerbation in the summer and the winter.<sup>1,2,3,4</sup> The differential diagnosis of PA includes vitiligo, morphea, tinea versicolor and nummular eczema.

Although clinicians are frequently faced with this condition, the literature is limited, partly because PA is mainly a cosmetic problem with lack of symptoms and, therefore, the patients fail to seek medical attention. For such reason a clinicopathologic study on PA was carried-out, and the results were compared with the existent literature.

## Materials and Methods

The study consisted of 20 patients seen in the Pediatric Dermatology clinic with the clinical diagnosis of PA. The clinical information obtained from each patient included age, sex, race, distribution of lesions, and family and personal history of atopy (including allergic rhinitis, bronchial asthma and atopic dermatitis). After informed



Figure 1. Hypopigmented patch on the cheek.

consent was taken, a skin biopsy of a typical lesion was performed in each patient. The skin biopsies were processed in our dermatopathology laboratory, stained with hematoxylin and eosin, and evaluated by the dermatopathologist.

## Results

There was an equal number of male and female patients with 10 in each group. There were 14 white patients and 6 black patients. The age ranged from 2 to 50 year-old, with a median of 10 years and a mean average of 12 years. Seventy five percent of the patients had a personal



history of atopy, with ten percent of the patients having a family history, and 15% showing neither family nor personal history of atopy. Ninety percent of the patients presented with lesions on their arms, 50% with lesions on the face, 40% with lesions on the legs and 25% with lesions on the trunk.

Upon histopathologic evaluation (Table I), spongiosis was found to be the most consistent finding being present in 85% of the patients. (Figure 2). Focal parakeratosis was seen in 45%, follicular spongiosis in 40% and mild acanthosis in 55%. In the dermis, the cellular infiltrate was always lymphocytic and perivascular, being sparse in 80% and moderate in 20%. Melanophages were seen in the upper dermis in 85% of the cases. Other findings included dilation of the superficial blood vessels in 30% and a mild upper dermal edema in 15% of the cases.

Table I

Pityriasis Alba  
Histopathology Summary

Parakeratosis	- 9/20 ( 45%)
Spongiosis	- 17/20 ( 85%)
Follicular Spongiosis	- 6/15 ( 40%)
Acanthosis	- 11/20 ( 55%)
Cellular Infiltrate:	
Perivascular	- 20/20 (100%)
Sparse	- 16/20 ( 80%)
Moderate	- 4/20 ( 20%)
Melanophages	- 17/20 ( 85%)

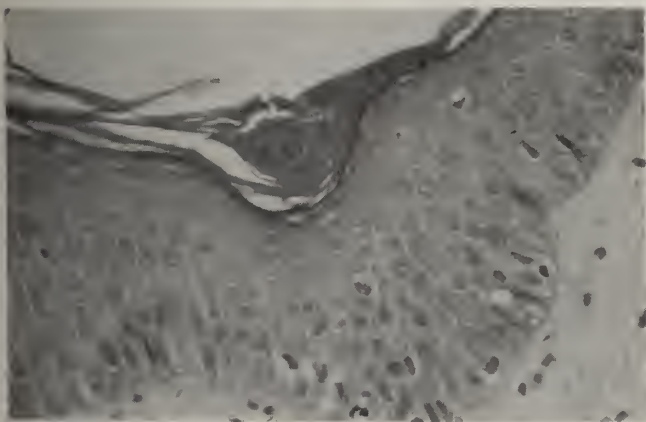


Figure 2. Focal spongiosis with parakeratosis.

### Comment

The first description of PA in the American literature was by Fox<sup>5</sup> in 1923 who presented three mulatto brothers with partially depigmented lesions in their faces. He was followed in 1924 by Pardo-Castello and Martínez Domínguez<sup>6</sup> who isolated the fungus *Aspergillus* from

the lesions of six out of thirty six patients and proposed the name of *achromia parasitaria* for the condition. Hazen<sup>7</sup> was the first to use the name of PA in 1927. In 1946, Dobes and Jones<sup>8</sup> isolated hemolytic streptococci from the lesions in five out of seven patients, and thus proposed the name of *erythema streptogenes*. Finally, in 1955 O'Farrell<sup>1</sup> dismissed an infectious etiology due to the lack of conclusive evidence and proposed to go back to the name of PA.

The etiology of PA is still unknown. It has been considered as a "group of persistent nonspecific erythema produced as a result of a localized inflammatory reaction, not related to fungi or bacteria, but with some relationship to dryness of the skin"<sup>2</sup> which as it is known, exacerbates the condition. In fact, Urano Suehisa and Hachiro Tagami in 1985 found a lower hydration state in the stratum corneum of lesions PA as compared with normal surrounding skin.<sup>9</sup> The studies done on extensive PA,<sup>10</sup> a clinical variant of PA, have shown a decrease in the amount of melanin as well as a decrease in the number of functional melanocytes in the epidermis of lesions of PA.

The largest series of PA was reported by Wells, Whyte and Kierland in 1960<sup>2</sup> from the Mayo Clinic. They studied 67 patients over a 10-year period, including 37 females and 30 male patients, 80% of them 15-years-old or less. They found the seasonal variation to be nonspecific with 36% of patients having exacerbation in the summer and 36% in the winter. Seasonal variation is difficult to evaluate in Puerto Rico where there is a stable climate throughout the year, although many patients referred exacerbation in the summer. The histologic evaluation in Wells' report was limited to three patients, in whom they consistently found variable degrees of hyperkeratosis and parakeratosis, mild acanthosis, epidermal thinning, along with moderate dilation of blood vessels, a mononuclear cell infiltrate and moderate upper dermal edema, findings which compare favorably with our study.

In 1983, Zaynoun et al<sup>10</sup> conducted a histologic, histochemical and ultrastructural study of extensive pityriasis alba. Using the split-DOPA technique they found a significant reduction in the amount of melanin in 87% of the cases. Focal spongiosis was found only in 25% of the cases, with a mild superficial perivascular inflammatory infiltrate in 50%, mild upper dermal edema in 13% and melanophages in only 38% of the cases. The differences between these findings and those from our study could be explained because extensive PA is a variant of classic PA which occurs most commonly in older children and young adults, has a more prolonged duration, and presents with generalized symmetric skin involvement, with less involvement of the face.<sup>10</sup> Histologic findings of extensive PA then, probably vary from those of classic PA.

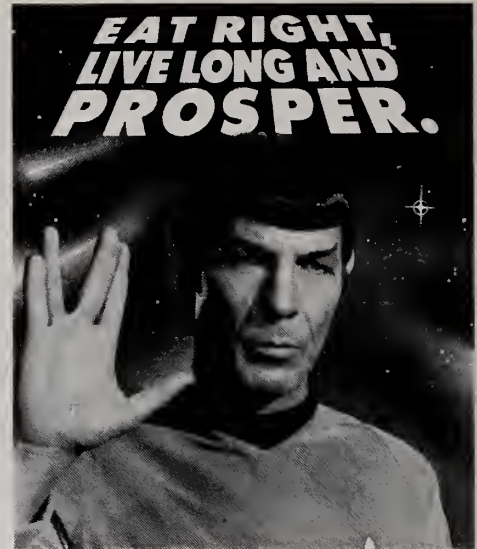
In conclusion, PA is a benign inflammatory condition of the skin characterized by the presence of hypopigmented macules of an unknown etiology. This study, which to our knowledge is the largest histopathologic series on PA, showed that this condition can be classified among the spongiotic processes with a possible relationship to atopy.

**Resumen:** Pityriasis alba es una enfermedad de la piel relativamente común que se caracteriza por máculas hipopigmentadas localizadas principalmente en las partes expuestas. Se reporta un estudio clinicopatológico de esta entidad que demostró una incidencia alta en preadolescentes con incidencia igual en niños y niñas y una predominancia de pacientes blancos sobre pacientes negros. Se encontró un historial personal frecuente de atopia y se observó que las lesiones de piel ocurrieron más frecuentemente en los brazos y la cara, seguidos por las piernas y finalmente el tronco.

La evaluación histológica demostró hallazgos consistentes de espongirosis y paraqueratosis focal, espongirosis folicular y acantosis en la epidermis junto a un infiltrado, perivascular linfocítico en la dermis superficial.

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# SPECIAL ARTICLES

## Leprosy in Puerto Rico: A Decade Later

Pablo I. Almodóvar, MD  
Judith Figueroa, RN, MPH

**Summary:** A study to evaluate the changes in the incidence and prevalence of leprosy in Puerto Rico was done to include the years 1981-1989. During this period, 75 new cases were diagnosed with an average of 8.3 cases per year. The yearly incidence was 1.9 cases per million which is significantly lower to the 4.6 per million in the previous study. At the present moment 182 cases are being followed at the Tropical Diseases Clinic of the University of Puerto Rico School of Medicine with a prevalence of 5.4 per 100,000 inhabitants. It is important to notice that 16 percent of the patients at the clinic were foreigners, a significant increase from a previous study. The decrease in the incidence of leprosy may be due to advances in the treatment of the disease and the new approach to integrate the patient into the community.

It is very difficult to state with accuracy the prevalence of leprosy in Puerto Rico. Different authors<sup>1-4</sup> have made tremendous efforts to gather and publish new data about the disease, that although not entirely accurate, gives a good idea about the problem.

The earliest reference to the disease was done by Fray Iñigo Abad in 1788<sup>1</sup> who observed that the disease was quite common at that time in the island of Puerto Rico. It was not until 1880 that a building in the rear of the district jail in Puerta de Tierra was built to house the persons with leprosy that roamed the streets. By 1899, there were ten lepers living in the institution who in October 17, 1900 were transferred to Isla de Cabras at the entrance to the harbor of San Juan. There is evidence that twenty one patients were isolated there by 1909. From 1900 to 1923 a total of 102 patients were admitted to the colony with an average of 4 new patients per year.

In 1926, the leper colony of 43 patients was moved from Isla de Cabras to the Insular Leprosarium in Trujillo Alto. For the next two decades the hospital kept a patient population between 50 and 60 until the mid forties when the modern era of chemotherapy began. During the period from 1926 to 1950 the new cases admitted to the Leprosarium reached 145 with an average of 6.5 new patients per year.<sup>2</sup>

In 1968 Nine Curt, Torres and Leopold<sup>3</sup> reported an extensive study covering a 25-year period from 1940 to 1964 and identified a total of 275 cases among surviving Puerto Ricans. The average new cases for that period was 6.9 per year. From 1967 to 1980, Vázquez-Botet, Sánchez and Ramos-Caro<sup>4</sup> reported 197 new cases during that 14-year period with an average of 14 new cases per year. For the first time, foreigners were a significant component of this group with 10.6 per cent of the total of new cases.

It is the purpose of this study to update our knowledge about the incidence and prevalence of leprosy and identify those factors which may have influenced them during the period 1981-89.

### Materials and Methods

The data for the 1981 to 1989 period was obtained from the following sources:

1. The Tropical Diseases Clinic- This is the Hansen's Disease Clinic at the University of Puerto Rico School of Medicine which is funded by the U.S. Public Health Service.

2. The National Hansen's Disease Program Registry at Carville, Louisiana.

The study includes Puerto Ricans and foreign born patients living or having their permanent residency in Puerto Rico. Three patients from the U.S. Virgin Islands, one of them Puerto Rican, who visit the clinic on a regular basis are also included.

The information obtained included name, age, sex, place of birth, present residential address, age at diagnosis, type or classification of the disease and family history of the disease.

### Results

A total of 75 new cases with leprosy were registered in Puerto Rico from 1981 to 1989 for an average of 8.3 new cases per year (Table I). Sixty percent of the new patients were classified in the lepromatous pole of the spectrum of the disease. The milder forms of the disease are less common. This figure corresponds to the overall distribution of all the patients seen at the Tropical Diseases Clinic where the lepromatous patients constitute 67 percent of the total of cases. The annual incidence of new cases during this period was 1.9 per million inhabitants which is lower than the 4.6 million per year reported from 1967 to 1980.

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Table 1

Annual Rate and Type of the Disease							
Year	LL	BL	BB	BT	TT	I	Total
1981	1	4	0	1	1	0	7
1982	6	5	0	0	1	0	12
1983	4	0	1	0	1	1	7
1984	1	2	0	0	3	2	8
1985	4	4	0	2	0	1	11
1986	1	1	0	2	0	0	4
1987	1	3	0	1	1	2	8
1988	0	2	0	0	2	1	5
1989	6	0	0	4	3	0	13
Total	24	21	1	10	12	7	75

LL - Lepromatous

BL - Bordeline Lepromatous

BB - Borderline

BT - Borderline Tuberculoid

TT - Tuberculoid

I - Indeterminate

A total of 182 cases are followed at the Tropical Diseases Clinic of the Department of Dermatology at the University of Puerto Rico School of Medicine. Table II shows the distribution of these patients with regard to nationality and type of disease. A total of 29 cases (16%) were foreigners. This figure represents a 6% increase from the previous study. There were eighteen patients from Santo Domingo and eleven from Colombia, Cuba, Venezuela, Lebanon and the U.S. Virgin Islands. The distribution of the different types of the disease is similar in both Puerto Ricans and foreigners.

Table III shows the distribution by sex and type of disease. Sixty per cent of the patients were male and forty percent were female.

Table 2

Place of Birth and Type of Disease				
Type	Puerto Rico	Dominican Republic	Other Countries	Total
LL	78	6	6	90
BL	27	4	2	33
BB	3	0	0	3
BT	11	2	1	14
TT	27	3	1	31
I	7	18	11	182
Total	153	18	11	182
	48%	10%	6%	

Table 3

Sex and Type of Disease				
Type	Males	Females	Total	
LL	55	35	90	49
BL	23	10	33	28
BB	2	1	3	2
BT	7	7	14	8
TT	18	13	31	17
I	5	6	11	6
Total	110	72	182	100
	60%	40%		

Table IV shows the age and sex distribution. The mean age was 54 years for both sexes. The majority of the patients are grouped in the 46-60 years group. Sixteen cases were reported in the 76-90 years group, which represents a nine percent of the total of patients.

Table 4

Age and Sex			
Age	Males	Females	Total
5-15	1	1	2
16-30	13	3	16
31-45	18	18	36
46-60	40	25	65
61-75	29	18	47
76-90	9	7	16
Total	110	72	182

## Discussion

Eventhough Puerto Rico is an island, it is very difficult to obtain accurate figures about the prevalence and incidence of leprosy. Since a significant percentage of our people have moved to the U.S.A., many of the cases identified as Puerto Ricans by the National Hansen's Disease Registry may be Puerto Ricans of second or third generation, and a few might be illegal aliens in the U.S.A. feigning to be Puerto Ricans.

The population in the island keeps increasing at a fast rate with an estimated 5.6% increase over the past decade. Many towns in the coastal zones have expanded and merge with others. At the present moment San Juan, Guaynabo, Trujillo Alto, Carolina, Bayamón and Cataño constitute the San Juan metropolitan area. Transportation is very accesible and people move constantly, living and working at different places. From the viewpoint of the incidence and prevalence of leprosy it is meaningless to try to divide the coastal zone in towns as it was done in the past.

The San Juan metropolitan area continues to be the area with the highest number of cases with forty five percent. Mayagüez comes second with 16% of the total of patients. Areas like Patillas, Naguabo and Ponce which showed a large incidence in the past, now have none or a few cases. Seven cases were identified in the towns in the central highlands: three in Morovis (mother and two sons), four in Caguas, and one case in San Sebastián. Most immigrants live in the San Juan metropolitan area and constitute 16 percent of the total number of new cases.

The prevalence of leprosy (number of cases per 100,000 inhabitants) in Puerto Rico was relatively constant until recently. In 1926 it was 10, in 1941 it was 11, in 1950 it was 9, in 1968 it was 8.7 and in 1980 it was 9 per 100,000. These figures included all cases with medical records at the Insular Leprosarium. During the period from 1981 to 1989 there was a total of 75 new cases with an average of 8.3 new cases per year and a prevalence of 5.4 per 100,000 inhabitants.



Most cases of leprosy are being followed at the Tropical Diseases Clinic and it is estimated that from 6 to 8 patients with leprosy are taken care of by dermatologists in private practice.

Recommendations to improve the surveillance and treatment of patients with leprosy were made in previous studies.<sup>4</sup> Since 1984, the Hansen's Disease Clinic became part of a national effort in the U.S.A. to eradicate the disease. The clinic has made a tremendous effort to localize all patients with this disease living in P.R. which are native Puerto Ricans or foreigners as well as those who have moved to the U.S.A. A screening program among relatives and close contacts of patients has identified a few more cases which includes most of the patients detected with indeterminate leprosy. Visits by the dermatology staff to endemic areas including lectures to physicians, nurses and lay people about early detection have not produced significant numbers of new leprosy patients. The main source of referrals is still from the dermatologists in the community. A functional record system with a computerized National Data Bank helps to keep track of patients moving to the different centers in the U.S.A. There is a full-time public health nurse to do screenings, sensory testing and visits to those patients who are unable to come to the clinic or who are lost to follow up. The patients who need corrective surgery are referred to the National Hansen's Disease Hospital in Carville, Louisiana. The patients get all the basic medications for their treatment and the medical care free of charge. In this sense, most of the recommendations suggested by the previous study have been implemented.

The data obtained in this study points toward a decrease in the incidence and prevalence of the disease. Leprosy patients are getting older and are dying from natural causes. The new cases diagnosed per year have decreased to less than half in the last decade and it is most probably due to the effectiveness of the treatment and the improvement on the socio-economical situation during the past two decades.

The new approach to follow these patients in an outpatient setting is helping in changing the attitude of the patients and society toward the disease. In sharp contrast to the persecution and forced isolation of yesteryear, today the leprosy patient is rendered non-infectious by medications and encouraged to remain an integral part of the community.

**Resumen:** El propósito de este estudio es evaluar si han ocurrido cambios en la incidencia y prevalencia de la enfermedad de lepra en Puerto Rico durante el período de 1981 a 1989. Durante este período de tiempo, se diagnosticaron 75 casos nuevos con un promedio anual de 8.3 casos por año. La incidencia anual fue de 1.9 casos por millón lo cual es significativamente menor a los 4.6 casos por millón en el estudio anterior. En la actualidad se mantienen 182 pacientes activos en la Clínica de Dermatología Tropical con una prevalencia de 5.4 casos por 100,000 habitantes.

Es importante notar que durante este período de tiempo el 16 por ciento de los pacientes que fueron diagnosticados eran extranjeros, un aumento significativo desde el estudio anterior.

Esta disminución en la incidencia de lepra puede significar que los avances en el tratamiento y nuevos enfoques hacia la enfermedad estén teniendo éxito.

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**Sevilla Moya, Pascual MD** - Escuela de Medicina de la Universidad Central del Este, República Dominicana, 1984. Medicina General. Ejerce en Mayagüez.

## INTERNOS-RESIDENTES

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**Description:** Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubiaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

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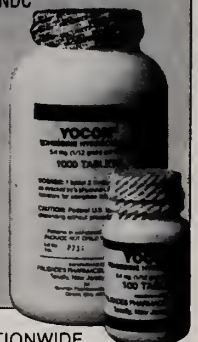
**Dosage and Administration:** Experimental dosage reported in treatment of erectile impotence.<sup>1,3,4</sup> 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.<sup>3</sup>

**How Supplied:** Oral tablets of Yocon<sup>®</sup> 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

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## AN AIDS-INFECTED SURGEON: NO EVIDENCE OF TRANSMISSION TO PATIENTS

A surgeon with AIDS who operated on thousands of patients apparently infected none of them, according to a study in the *Journal of the American Medical Association*.

In January 1989, local media in Nashville, Tenn., reported that a general surgeon had been recently diagnosed with AIDS, according to Ban Mishu, MD, of the Division of Field Services, Centers for Disease Control, Atlanta, Ga., and colleagues. Later that month he died of AIDS-related respiratory failure.

Shortly after the publicity began, questions arose about whether he could have infected his patients while operating. His practice had been a busy one—he performed about 300 operations a year at three local hospitals.

Researchers identified 2,160 patients who underwent surgery by the physician since 1982. None had been reported to the Tennessee AIDS registry; 264 already had died (none of AIDS- or HIV-related diseases). Of the 1,896 patients remaining, 1,652 were contacted, the authors write, and 37 percent were tested.

Only one patient, a known IV-drug user and regular client of prostitutes, was HIV antibody positive, they note.

"These results support the concept that the risks to patients operated on by HIV-infected surgeons are most likely quite low," the authors write.

Given the fact the surgeon wasn't diagnosed with AIDS until January 1989, researchers estimate he could have been infected as early as 1982 and, therefore, traced his patients back that far.

"We attempted to notify and offer HIV antibody testing to all patients who had been operated on by the surgeon with AIDS during the seven years before his diagnosis," the authors conclude. "No evidence of HIV transmission to patients of this surgeon was detected in our study."

There have been a few other studies concerning potential HIV transmission from health care workers to patients, but according to the authors, this study "remains the largest of its type and may provide the best data for some time to come."

They also say the results of their study support the notion that HIV infections among health care workers should be reviewed on a case-by-case basis.

In an accompanying editorial, Frank S. Rhame, MD, of the Department of Medicine at the University of Minnesota, Minneapolis, says surgeons who don't face constant exposure to needle sticks (such as ophthalmic surgeons) probably need not be tested. The editorialist also estimates there probably are "hundreds of practicing surgeons" who are HIV-infected and said the issues faced in Nashville "will undoubtedly arise in many U.S. hospitals."

Rhame estimates the probability of surgeon-to-patient HIV infection to be between one per 100,000 and one per million operations.

"What should hospitals do regarding patients who have been operated on by a surgeon who is found to be HIV infected?" he asks.

At the University of Minnesota Hospital, surgeons are required to determine their HIV status "only if they are at an increased risk of HIV infection," he writes. If they are infected, surgeons are required to avoid surgery that requires "blind, by-feel manipulation of sharp instruments."

*JAMA July 25, 1990*

## MORE PHYSICIAN INVOLVEMENT NEEDED IN PUBLIC HEALTH ISSUES: AMA COUNCIL

Practicing physicians and public health officials should bury the hatchet, says a report in the *Journal of the American Medical Association*.

Tension between private practitioners and public health professionals dates back to the turn of the century, according to the AMA Council on Scientific Affairs, author of the report. More dialogue and cooperation between the two sectors is needed to address problems such as indigent medical care, injuries, and Alzheimer's disease, the Council says.

Physicians should "work cooperatively with public health professionals, strengthen public health services, and ensure health services of good quality for all citizens," the Council urges.

The Council report echoes a number of the recommendations set forth in an Institute of Medicine report entitled "The Future of Public Health."

Private physicians and those in public health often differ from one another in training, philosophy and practice. The split between the two groups can be traced back a hundred years, when the numbers of physicians rose and there was increased competition from dispensa-

ries, well-child clinics, and settlement houses. Some physicians resisted public health regulations such as requiring the reporting of tuberculosis and syphilis cases.

In the 1920s the rift widened as public health physicians voiced their support for national health insurance, a difference which continues to this day.

Private practitioners may also believe public health officers are incapable of performing routine clinical procedures. Public health doctors, on the other hand, "may view the private practitioner as more of a businessperson than a physician," says the Council. "It is likely that many persons in both groups do not understand the essential significance of the other group to the community's well being," it writes.

Practicing physicians could share their experience in using different treatment regimens with their public health colleagues.

The council's other recommendations include:

- clinicians should volunteer to assist their community public health department;
- increasing dialogue, interchange and cooperation between the leadership of both sectors;
- greater emphasis on public health issues in medical school;

"Clearly, working together in the society's best interests is a crucial goal in these times," writes Roger J. Bulger, MD, president of the Association of Academic Health Centers, Washington, D.C., in an accompanying editorial. "To do so requires trust and understanding sufficient to accord to the other party the freedom to think as he or she will about financial matters or political strategies."

In Bulger's view, "the most fundamental issue separating the medical clinician from the public health practitioner is the differing scientific paradigms under which they operate and conceptualize their activities." While clinicians focus on patient-specific interventions, public health physicians take a more global view of illness and mortality. But, he concludes, "each field needs the other."

*JAMA July 25, 1990*

#### PAINTER VAN GOGH HAD MENIERE'S DISEASE

One hundred years after his suicide, researchers have concluded that painter Vincent Van Gogh suffered not from epilepsy and madness, but from Meniere's disease, according to an article in the *Journal of the American Medical Association*.

Van Gogh, known for his vivid works and his tortured life, which included a famous incident in which he cut off part of his left ear and gave it to a prostitute. In May 1889, Van Gogh voluntarily committed himself to a French asylum for epileptics and lunatics. The physician there wrote, "It is my opinion that M. Van Gogh is subject to epileptic fits at very infrequent intervals."

After a review of 796 of Van Gogh's personal letters, I. Kaufman Arenberg, MD, of Swedish Medical Center, Englewood, Colo., and colleagues, conclude that "the

clinical descriptions in his letters are those of a person suffering from Meniere's disease, not epilepsy."

Meniere's disease is a disorder of the inner ear characterized by recurrent vertigo, deafness and tinnitus, a ringing or buzzing in the ear.

The asylum physician's statement formed the basis of the epilepsy diagnosis, "but no rigid criteria were ever described," the authors write. The letters, written between 1884 and 1890, "clearly describe disabling attacks of 'vertigo' typical of labyrinthine vertigo, accompanied by nausea and vomiting and noise intolerance and separated by symptom-free periods."

In his letters, Van Gogh described violent attacks of vertigo. "During the attacks," Van Gogh wrote "I feel a coward before the pain and suffering." Since Meniere's disease had been known of for at least 30 years prior to Van Gogh's institutionalization, "that he was diagnosed as an epileptic reflects a lack of dissemination of state-of-the-art medical knowledge from Paris to the smaller cities in the provinces," the authors write.

According to the authors, Van Gogh's "voluntary admission to the asylum at St. Remy, hoping to find help for his attacks of vertigo that everyone else thought was a form of epilepsy (epileptoid) and his rational behavior at the asylum as well as before and after attacks as described in his voluminous correspondence, should forever banish the notion that he was an epileptic or 'mad.'"

*JAMA July 25, 1990*

#### COMBINATION DRUG THERAPY PREVENTS RECURRENT URINARY TRACT INFECTION

A study in the *Journal of the American Medical Association* offers some hope to women who suffer frequent urinary tract infections after sexual intercourse.

A combination of antimicrobial drugs taken after sex may protect women from recurrent urinary infections regardless of how often they have intercourse, concludes Ann Stapleton, MD, of the Department of Medicine, University of Washington, Seattle, and colleagues. The treatment "may be especially beneficial to women using a diaphragm for contraception, since the device has been blamed for contributing to the infections, say the authors.

The researchers compared the efficacy of 40 mg trimethoprim/200 mg sulfamethoxazole (commonly sold under the trade names Bactrim or Septra) versus placebo administered after intercourse in a double-blind study design. Sixteen women took the drug combination after sex and 11 took placebo. The average age of the women in the study was 23 years.

Sixty-nine percent of women in the drug group used diaphragms versus 91 percent in the placebo group. All of the women enrolled in the study had at least two urinary tract infections confirmed via culture in the past year.

All patients were free of infection at the beginning of the study. After six months, nine of the 11 women in the placebo group developed urinary tract infections (infection rate, 3.6 per patient-year). In the drug group, only two of 16 women developed infections (infection



rate, 0.3 per patient-year). The cumulative proportion of patients who remained infection free was significantly greater in the group that used postcoital trimethoprim-sulfamethoxazole than in the placebo group.

"Our data demonstrate that postcoital trimethoprim-sulfamethoxazole is highly effective in preventing recurrent urinary tract infection in infection-prone young women with a history of frequent (two or more) infections in the preceding year," say the authors.

The researchers also investigated the relationship between intercourse frequency and the prophylactic effect of drug therapy. Among women taking the placebo, more frequent intercourse was significantly correlated with increases in infection rate. In the drug group, postcoital therapy was effective regardless of the frequency with which the women had sex.

"This finding supports prior reports that suggest that sexual intercourse increases the risk of urinary tract infection in women," say the authors.

In view of their findings, the authors recommend continuous drug prophylaxis for women who have three or more urinary tract infections per year. In women who have one or two infections per year, continuous therapy is not desirable, and "either intermittent self-treatment or postcoital prophylaxis...might be preferable," they conclude.

*JAMA August 8, 1990*

#### GEOGRAPHIC DISTRIBUTION OF INCIDENCE OF HIP FRACTURES IN UNITED STATES

Here's a strange, unexplained medical fact: more elderly white women older than 65 years break their hips in southern states than their northern counterparts, according to a study in the *Journal of the American Medical Association*. Several theories exist, but none has been supported with definitive evidence, according to Steven J. Jacobsen, PhD, of the Epidemiology Program, School of Public Health, University of Illinois, Chicago, and his colleagues. The authors reviewed Department of Veterans Affairs hospital records of elderly white women with hip fractures, aged 65 years and older, from 1984 through 1987. The study notes the U.S. is the second-leading region in the numbers of hip fractures among the elderly (Scandinavia is first), but the authors note that until now, few studies have looked at geographic differences within American. While higher hip fracture rates were found in various counties in northern states, southeastern states saw the highest cluster of hip fractures in elderly white women, the authors note. "No presently recognized factor or factors adequately explain this observed geographic variation," the authors conclude.

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#### GAPS EXIST IN PHYSICIANS' KNOWLEDGE ABOUT RISK OF BLOOD TRANSFUSIONS: STUDY

"Widespread deficiencies" in physicians' knowledge of transfusion risks exist among surgeons, orthopedic surgeons and anesthesiologists surveyed, according to a

study in the *Journal of the American Medical Association*. Each transfusion risk discussed during a face-to-face survey was estimated correctly by less than half of the physicians questioned, write Susanne R. Salem-Schatz, ScD, of the Program for the Analysis of Clinical Strategies, Harvard Medical School and Beth Israel Hospital, Boston, Mass., and her colleagues. "We were surprised by the degree to which physicians incorrectly estimated transfusion-associated risks, given our intention of defining generous correct response ranges," they write. The researchers questioned 122 physicians in three hospitals and found that the more years of experience a physician had, the less he or she knew about transfusion risks. Six out of ten resident physicians said they ordered transfusions at least once a month that they felt were unnecessary because more senior physicians suggested they do so. Almost half (44 percent) of those surveyed said they were not aware of guidelines established either by a blood bank or hospital administration regarding ordering and transfusion of blood products, the study says. And of physicians who said they were aware of guidelines, 46 percent said the restrictions had little or no influence on their transfusion decisions. The researchers also found that "physicians with the least knowledge demonstrated the greatest confidence."

*JAMA July 25, 1990*

#### RESTING METABOLIC RATE UNAFFECTED BY DIETING

Growing concern that dieting may work against itself by lowering a dieter's resting metabolic rate doesn't appear to be warranted, according to a study in the *Journal of the American Medical Association*.

Studying women who used a very-low-calorie diet program (Optifast) and those who followed a less drastic regimen, researchers found no long-term reductions in resting metabolic rates (RMR) "that exceeded decreases anticipated with the achievement of a lower body weight," according to Thomas A. Wadden, PhD, of the Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, and his colleagues.

Previous studies have concluded some diets result in a drop in resting metabolic rates, which contributes to subsequent regaining weight, but the current study failed to confirm those data.

"We cannot agree that dieting combined with modest physical activity is associated with long-term reductions in RMR that exceed decreases anticipated with the achievement of a lower body weight," the authors write.

Nine times during a 48-week study period, 18 obese women had their resting metabolic rates measured. One group of nine women was limited to a 1,200-kcal daily diet for the entire study while the second group of nine women was restricted to a very-low-calorie plan of 420 kcal every day, the study said. They maintained that very-low-calorie intake for 16 weeks, then gradually returned to a solid-food diet.

Patients in both groups increased their physical activity, principally through walking, the authors said.

Significant changes in resting metabolic rates took place during the first five weeks of both groups. The RMR fell 10.3 percent for those in the 1,200-kcal diet during that time and 21.2 percent for those using the Optifast very-low-calorie diet. When the Optifast dieters resumed a more normal diet, their resting metabolic rates rose sharply. By week 48, their RMR was only 9.1 percent lower than it was at the beginning of the study, the authors write.

And at the end of the study, the RMR for those on a less drastic diet at the end of the study was only 10.9 percent below the levels they were at the start, the study adds.

"End-of-treatment changes in the resting metabolic rate per kilogram of fat-free mass did not differ significantly from baseline in either condition," the authors write.

The average woman in the study weighed about 216 pounds at the time the study began, and the participants averaged 38 years of age. Optifast patients lost about twice as much weight as those in the less-drastic diet at all periods during the first 25 weeks of the study. At week 17, Optifast patients showed a mean weight loss of approximately 47 pounds, compared to an approximate 22-pound weight loss for the 1,200-kcal daily dieters.

The authors suggest that achieving a long-term rebound in resting metabolic rate may be helped by increased physical activity during dieting.

"Weight loss achieved by the combination of diet and exercise as well as by exercise alone may be associated with more favorable long-term changes in RMR than is weight loss achieved by diet alone," they write.

*JAMA August 8, 1990*

### INCREASED SURGERY RISK FROM CLOT-DISSOLVING DRUGS AFTER HEART ATTACK IS REASONABLE: STUDY

Drug therapy used to dissolve potentially lethal blood clots in the coronary arteries of heart attack victims has been shown in the short run to increase the need for arterial surgery. An article in the *Journal of the American Medical Association* says the surgery is reasonable, given the benefits of the therapy.

Intravenous drug therapy to dissolve the blood clots, called thrombi, "reduces short- and long-term mortality from acute myocardial infarction and clearly deserves wide application," write authors C. David Naylor, MD, DPhil, of the Sunnybrook Health Science Centre, North York, Canada, and Susan B. Jagal, MSc, Graduate Department of Community Health, University of Toronto, Canada. Untreated blood clots can block a coronary artery, choking off blood flow to heart muscle tissue.

While the drug therapy, called intravenous thrombolysis, dissolves the clots, it does not remove the underlying atherosclerotic lesions, the authors write. The lesions narrow the artery, limiting blood flow and endangering the otherwise viable heart muscle tissue. To reduce that risk, one of two surgical revascularization procedures are often done: coronary artery bypass surgery (CABS) or

percutaneous transluminal coronary angioplasty (PTCA).

The authors analyzed data from seven studies that included patients hospitalized in Australia, Canada, Germany, New Zealand, Switzerland and the United States. They found an 80 percent increase in revascularization procedures among patients who had undergone intravenous thrombolysis. Only procedures done within the first six weeks after the heart attack were included in the study.

"The demonstrated increase in the use of CABS and PTCA should not be seen as a drawback to thrombolytic therapy or as indicative of unnecessary intervention but is instead likely to represent a reasonable investment to consolidate immediate gains from lysing occlusive thrombi in infarct-related coronary arteries," they write.

In an accompanying editorial, Robert C. Schlant, MD, from the Department of Medicine, Emory University School of Medicine, Atlanta, Ga., write "the early use of thrombolytic therapy clearly saves a substantial number of lives, but, over the next several weeks, a substantial number of patients will manifest angina pectoris at rest or will have evidence of myocardial ischemia during an exercise test...Some patients requiring such revascularization therapy may well have died without thrombolytic therapy or might have sustained significant myocardial damage, potentially requiring extensive and expensive medical care.

"Thus, early thrombolytic therapy of patients with acute myocardial infarction saves myocardium and saves lives and may provide a window of opportunity to identify selected patients for revascularization procedures that lessen the likelihood of recurrent infarction or death."

*JAMA August 8, 1990*

### SURGERIES FOR EPILEPSY GROWING FOR CHILDREN AND ADULT PATIENTS

With the hope for better lives, a "rapidly increasing" number of epileptics are undergoing brain surgeries nationwide, according to a report in the *Journal of the American Medical Association*.

Several medical centers are reporting success with the brain surgeries designed to treat epileptics when their anticonvulsant drug therapies fail to alleviate symptoms, according to the consensus conference report, sponsored by the National Institute of Neurological Disorders and Stroke, and the Office of Medical Applications of Research of the National Institutes of Health in Bethesda, Md.

The conference, which convened on March 19-21 of this year, considered questions ranging from what patients should undergo surgery to what criteria should be used to determine the procedures' success.

Persons with "intractable epilepsy" can be candidates for surgery after a number of steps have been taken, including detailed medical examinations and a definitive conclusion has been reached that drug therapies haven't worked.



"There is no precise definition of intractable epilepsy," the report says. "Among the considerations are seizure frequency, seizure type, severity of attacks, and impact on quality of life. If a patient falls during seizures that occur only a few times a year, repeated injuries and trips to emergency departments can make life miserable."

Another reason to consider surgery, according to the report, is that repeated seizures may have adverse effects on the brain which can lead to progressive brain function deterioration. Also, long-term use of anticonvulsant drugs "may cause toxic syndromes and may also have adverse effects on learning, scholastic achievement, development and job performance."

The report's authors warn, however, epilepsy surgery is not without its own problems.

There are no large-scale clinical trial test results to confirm the effectiveness of brain surgeries for epilepsy; there are differences of opinion over what surgical methods should be used; and costs can range from \$25,000 to more than \$100,000 for diagnostic evaluation and surgery.

Right now, the report says, about 500 patients undergo brain surgery for their epilepsy annually. But experts estimate that between 2,000 and 5,000 new U.S. patients may be candidates for similar procedures every year.

In a related report, Sumio Uematsu, MD, of the Johns Hopkins Epilepsy Center and Department of Neurosurgery, The Johns Hopkins University School of Medicine, Baltimore, Md., discusses the case of a 23-year-old woman with a history of uncontrollable complex partial epileptic seizures.

After receiving a smallpox vaccination at 18 months of age, she experienced two seizures, the author writes. Treated with phenobarbital, she did not demonstrate further symptoms until she was six years old. High drug dosages and several different drugs were used to try and treat recurring seizures.

About a year and a half ago, Uematsu performed surgery on the patient. The author reports since the surgery, "no complex partial or generalized seizures" have occurred.

"We plan to maintain minimal anticonvulsant medications for two years and then discontinue this therapy as tolerated," the author concludes.

*JAMA August 8, 1990*

#### DRUG THERAPY FOR ORGANIC IMPOTENCE CALLED SAFE, EFFECTIVE BY AMA PANEL

Men suffering from impotence caused by physical, not psychological, problems can be treated successfully by injection of drugs into the penis. In the *Journal of the American Medical Association*, the AMA Diagnostic and Therapeutic Technology Assessment (DATTA) panel concludes that papaverine alone or in combination with phentolamine injected into the penis is safe and effective for treating organic impotence. Patients with neurogenic impotence have the greatest success rates. The drugs are injected by the patient, producing an erection lasting from 10 minutes to 2 hours. Persistent erection is the most common short-term side effect. The DATTA panel expressed concern that the treatment may cause long-term liver damage or distort the shape of the penis by formation of scar tissue at the injection site.

*JAMA August 8, 1990*

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**Warnings: Angioedema.** Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

**Hypotension:** Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Patients with heart failure given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. Caution should be observed when initiating therapy. (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

**Neutropenia/Aggranulocytosis:** Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

**Precautions: General Impaired Renal Function.** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

**Evaluation of patients with hypertension or heart failure should always include assessment of renal function.** (See DOSAGE AND ADMINISTRATION.)

**Hyperkalemia:** Elevated serum potassium (>5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See Drug Interactions.)

**Surgery/Anesthesia:** In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

**Information for Patients:**

**Angioedema:** Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

**Hypotension:** Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

**Hyperkalemia:** Patients should be told not to use salt substitutes containing potassium without consulting their physician.

**Neutropenia:** Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

**NOTE:** As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

**Drug Interactions:**

**Hypotension: Patients on Diuretic Therapy:** Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

**Agents Causing Renin Release:** The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

**Other Cardiovascular Agents:** VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyl-dopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

**Agents Increasing Serum Potassium:** VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

**Lithium:** Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

**Pregnancy—Category C:** There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radiography was found to cross the placenta following administration of labeled enalapril to pregnant hamsters. There are no adequate and well-controlled studies of enalapril in pregnant women. However, data are available that show enalapril crosses the human placenta. Because the risk of fetal toxicity with the use of ACE inhibitors has not

been clearly defined, VASOTEC® (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome. Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality.

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypotension, or the underlying prematurity.

**Nursing Mothers:** Milk in lactating rats contains radioactivity following administration of <sup>14</sup>C enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

**Pediatric Use:** Safety and effectiveness in children have not been established.

**Adverse Reactions:** VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

**HYPERTENSION:** The most frequent clinical adverse experiences in controlled trials were headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

**HEART FAILURE:** The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

**Cardiovascular:** Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, Hypotension); pulmonary embolism and infarction, pulmonary edema; rhythm disturbances, atrial fibrillation, palpitation.

**Digestive:** Ileus, pancreatitis, hepatitis (hepatocellular or cholestatic jaundice), melena, anorexia, dyspepsia, constipation, glossitis, stomatitis, dry mouth.

**Musculoskeletal:** Muscle cramps.

**Nervous/Psychiatric:** Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

**Urogenital:** Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

**Respiratory:** Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection.

**Skin:** Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pruritus, alopecia, flushing, hyperhidrosis.

**Special Senses:** Blurred vision, taste alteration, anosmia, tinnitus, conjunctivitis, dry eyes, tearing.

A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgias, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash, and other dermatologic manifestations.

**Angioedema:** Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

**Hypotension:** In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

**Clinical Laboratory Test Findings:**

**Serum Electrolytes:** Hyperkalemia (see PRECAUTIONS), hyponatremia.

**Creatinine, Blood Urea Nitrogen:** In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

**Hemoglobin and Hematocrit:** Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3% and 1.0 vol %, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC. These are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

**Other (Causal Relationship Unknown):** In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported. A few cases of hemolysis have been reported in patients with G6PD deficiency.

**Liver Function Tests:** Elevations of liver enzymes and/or serum bilirubin have occurred.

**Dosage and Administration:** Hypertension. In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed. If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

**Dosage Adjustment in Hypertensive Patients with Renal Impairment:** The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

**Heart Failure:** VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects.) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

**Dosage Adjustment in Patients with Heart Failure and Renal Impairment or Hyponatremia:** In patients with heart failure who have hypotension (serum creatinine > 30 mg/dL) or hyponatremia (serum sodium < 130 mEq/L), therapy should be initiated at a lower mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, Heart Failure, WARNINGS, and PRECAUTIONS, Drug Interactions.) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

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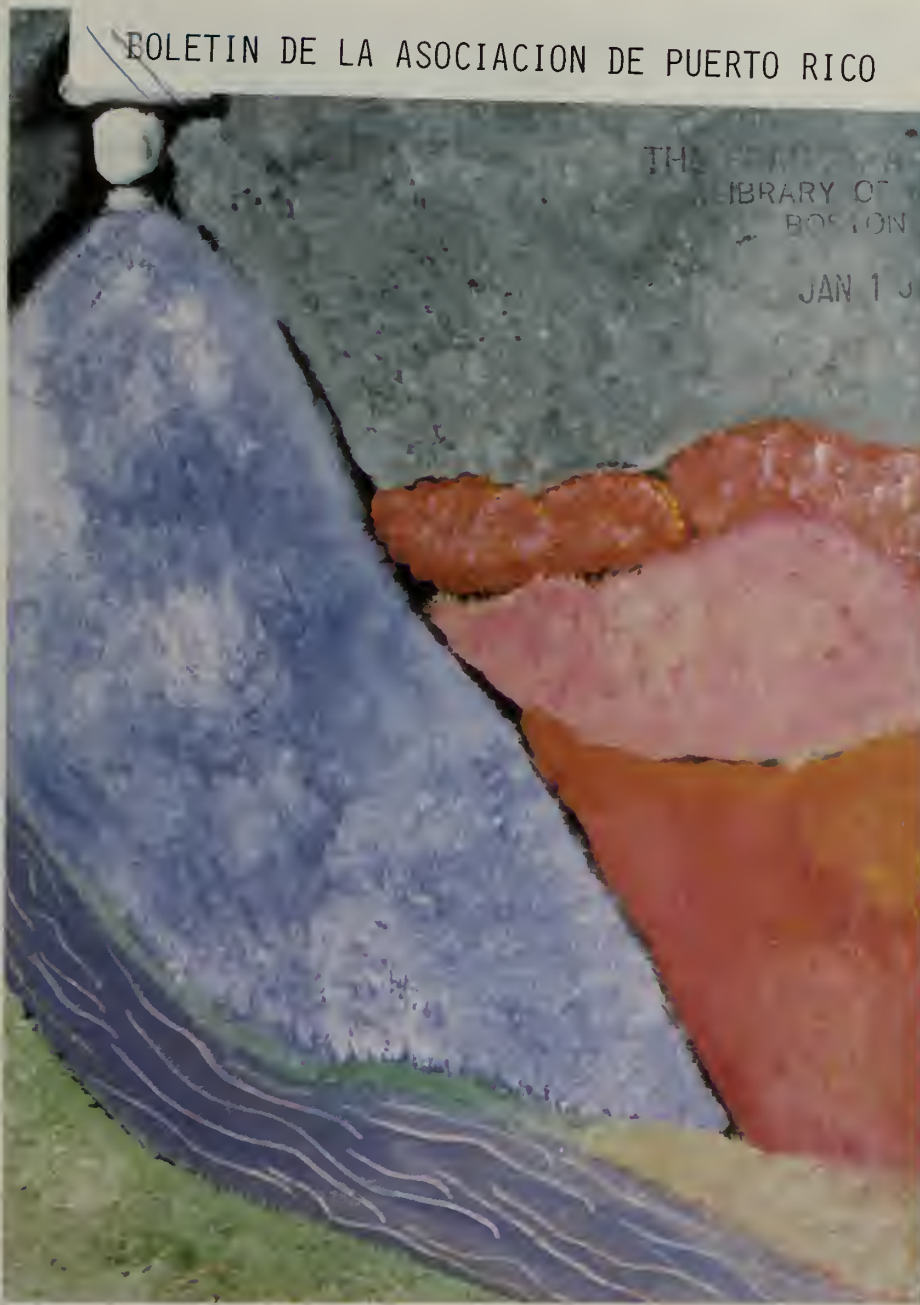
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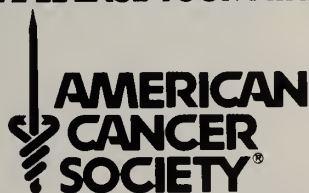
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## *Nuestra Portada*

**La Montaña de la Casa de los Poetas.** Obra del artista puertorriqueño Pablo Romero. El autor es natural de Santurce, Puerto Rico y sus obras pictóricas figuran en numerosas colecciones. Entre las más conocidas están el Museo Metropolitano de Nueva York, Museo del Bronx, el Ateneo Puertorriqueño y el Museo del Barrio en Nueva York. Recientemente sus obras fueron expuestas en la Sexta Bienal del Retrato Contemporáneo en Tuzla, Yugoslavia.

La obra de la portada es parte de una serie titulada *La Casa de los Poetas*. Esta serie representa el quehacer creativo de cada individuo visto desde su propio mundo (su casa) y el proceso de crecimiento de cada persona.

La Montaña de la Casa de los Poetas pertenece a la colección privada del Dr. Manual R. Pérez-González, Radiólogo que ejerce en Santurce. La Junta Editora del Boletín de la Asociación Médica de Puerto Rico le agradece al Dr. Pérez-González su colaboración con nuestra revista.

# EDITORIAL



*La medicina y la moral descansan sobre una base común: sobre el conocimiento físico de la naturaleza humana.*

*Seneca*

**L**a práctica de la medicina en Puerto Rico se ha desarrollado en varias áreas al nivel de la práctica de la medicina en diferentes centros médicos de excelencia del exterior.

Estamos conscientes que el avance de la medicina ha sido el resultado de un extraordinario esfuerzo de nosotros, los puertorriqueños, a pesar de ciertas limitaciones económicas y geográficas.

Nos alienta el hecho que un grupo de médicos y profesionales relacionados a nuestra Institución participen en la publicación de este número del Boletín de la Asociación Médica durante la celebración de nuestro Décimocuarto Aniversario. A cada uno de los autores le damos las gracias y a la vez los estimulamos a continuar, junto con los participantes de los últimos tres años, a perpetuar la publicación de artículos médicos relacionados con el Centro Médico San Pablo.

Tanto la Junta de Directores, la Facultad Médica y este servidor, agradecemos la oportunidad brindada por la Junta Editora del Boletín de la Asociación Médica de Puerto Rico en la publicación de este número.

Dr. Pedro M. Mayol, FAAP, FCCP  
Director Médico  
Centro Médico San Pablo



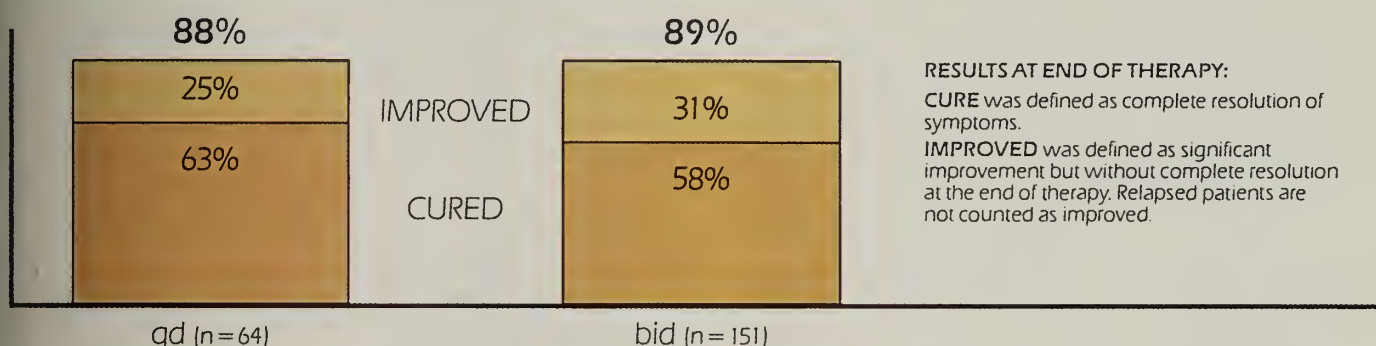
# THE FIRST ORAL THIRD GENERATION CEPHALOSPORIN FOR OTITIS MEDIA\*

Once-Daily Dosing Maintains Inhibitory Drug  
Concentrations Against Important Pathogens in Otitis Media

SUPRAX Oral Suspension Provides Outstanding Clinical and  
Bacteriologic Success in Otitis Media<sup>4,5</sup>

Excellent Clinical Success in Otitis Media†

191 of 215 Patients Effectively Treated qd or bid With 10-Day Course of  
SUPRAX Oral Suspension‡



The Only Cephalosporin Indicated for  $\beta$ -Lactamase Producing  
Strains of Haemophilus influenzae and Branhamella catarrhalis

The Only Once-a-Day for Otitis Media

Convenient Dosing and Flexibility

- 8 mg/kg per day in children regardless of severity of infection
- Administered once or twice daily with or without food

\* Due to susceptible organisms. Please consult **Clinical Studies** section of brief summary for limitations on usage.

† Results of clinical trials in infections due to *Haemophilus influenzae*, *Branhamella catarrhalis*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae*. Please consult **Clinical Studies** section of brief summary for limitations on usage.

‡ Tablets should not be substituted for suspension in otitis media.

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NEW

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**BRIEF SUMMARY.** Please see package insert for full Prescribing Information  
**INDICATIONS AND USAGE**

Otitis Media caused by *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Moraxella (Branhamella) catarrhalis*, (most of which are beta-lactamase positive), and *Streptococcus pyogenes*.

**Note:** For information on otitis media caused by *Streptococcus pneumoniae*, see **CLINICAL STUDIES** section.

Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* (beta-lactamase positive and negative strains).

Perform culture and susceptibility studies to determine causative organism and its susceptibility to SUPRAX. Therapy may begin while waiting for study results and may be adjusted when results are known.

Pharyngitis and Tonsillitis caused by *Streptococcus pyogenes*.

**Note:** Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* infections, including the prophylaxis of rheumatic fever. SUPRAX is generally effective in the eradication of *S. pyogenes* from the nasopharynx; however, data establishing the efficacy of SUPRAX in the subsequent prevention of rheumatic fever are not available.

Uncomplicated Urinary Tract Infections caused by *Escherichia coli* and *Proteus mirabilis*.

\*Efficacy for this organism was studied in fewer than ten patients with otitis media.

#### CLINICAL STUDIES

In clinical trials of otitis media in nearly 400 children between the ages of 6 months to 10 years, *Streptococcus pneumoniae* was isolated from 47% of the patients, *Haemophilus influenzae* from 34%, *Moraxella (Branhamella) catarrhalis* from 15%, and *Streptococcus pyogenes* from 4%.

The overall response rate of *Streptococcus pneumoniae* to cefixime was approximately 10% lower and that of *Haemophilus influenzae* or *Moraxella (Branhamella) catarrhalis* approximately 7% higher (12% when beta-lactamase positive strains of *H. influenzae* are included) than the response rates of these organisms to the active control drugs.

In these studies, patients were randomized and treated with either cefixime at dose regimens of 4 mg/kg bid or 8 mg/kg qd, or with a standard antibiotic regimen. Sixty-nine to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated two to four weeks posttreatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs (18% including those patients who had *Haemophilus influenzae* resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the two- to four-week follow-up, a total of 30%-31% of patients had evidence of either treatment failure or recurrent disease.

Organism	Bacteriological Outcome of Otitis Media at Two- to Four-Weeks Posttherapy Based on Repeat Middle Ear Fluid Culture or Extrapolation from Clinical Outcome		
	Cefixime <sup>(a)</sup> 4 mg/kg bid	Cefixime <sup>(a)</sup> 8 mg/kg qd	Control <sup>(a)</sup> drugs
<i>Streptococcus pneumoniae</i>	48/70 (69%)	18/22 (82%)	82/100 (82%)
<i>Haemophilus influenzae</i> beta-lactamase negative	24/34 (71%)	13/17 (76%)	23/34 (68%)
<i>Haemophilus influenzae</i> beta-lactamase positive	17/22 (77%)	9/12 (75%)	1/1 <sup>(b)</sup>
<i>Moraxella (Branhamella)</i> <i>catarrhalis</i>	26/31 (84%)	5/5	18/24 (75%)
<i>Streptococcus pyogenes</i>	5/5	3/3	6/7
All Isolates	120/162 (74%)	48/59 (81%)	130/166 (78%)

<sup>(a)</sup> Number eradicated/number isolated

<sup>(b)</sup> An additional 20 beta-lactamase positive strains of *Haemophilus influenzae* were isolated, but were excluded from this analysis because they were resistant to the control antibiotic. In nineteen of these the clinical course could be assessed, and a favorable outcome occurred in 10. When these cases are included in the overall bacteriological evaluation of therapy with the control drugs, 140/185 (76%) of pathogens were considered to be eradicated.

Tablets should not be substituted for suspension when treating otitis media.

#### CONTRAINDICATIONS

Known allergy to cephalosporins.

#### WARNINGS

**BEFORE THERAPY WITH SUPRAX IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO SUPRAX OCCURS, DISCONTINUE THE DRUG. SERIOUS, ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.**

Administer cautiously to allergic patients.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of severe antibiotic-associated diarrhea including pseudomembranous colitis. Pseudomembranous colitis has been reported with the use of SUPRAX and other broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins). It is important to consider this diagnosis in patients who develop diarrhea in association with antibiotic use. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment and may range in severity from mild to life threatening. Mild cases usually respond to drug discontinuation alone. Moderate-to-severe cases should be managed with fluid, electrolyte, and protein supplementation. When the colitis is not relieved by drug discontinuation, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be excluded.

#### PRECAUTIONS

**General:** Prolonged use may result in overgrowth of nonsusceptible organisms. If superinfection occurs, take appropriate measures.

Carefully monitor patients on dialysis. Adjust dosage of SUPRAX in patients with renal impairment and those undergoing continuous ambulatory peritoneal dialysis and hemodialysis. (See **DOSE AND ADMINISTRATION**.)

Prescribe cautiously in patients with a history of gastrointestinal disease, particularly colitis.

**Drug Interactions:** No significant drug interactions have been reported to date.

**Drug/Laboratory Test Interactions:** A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferrocyanide.

SUPRAX cefixime administration may result in a false-positive reaction for glucose in the urine using Clinistest<sup>®</sup>, Benedict's solution, or Fehling's solution. Use glucose tests based on enzymatic glucose oxidase reactions [such as Clinistix<sup>®</sup> or Tes-Tape<sup>®</sup>].

A false-positive direct Coombs test has been reported during treatment with other cephalosporin antibiotics; therefore, it should be recognized that a positive Coombs test may be due to the drug.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Although no lifetime animal studies have been conducted to evaluate carcinogenic potential, no mutagenic potential of SUPRAX was found in standard laboratory tests. Reproductive studies revealed no fertility impairment in rats at doses up to 125 times the adult therapeutic dose.

**Usage in Pregnancy:** Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of harm to the fetus due to SUPRAX.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Labor and Delivery:** SUPRAX has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

**Nursing Mothers:** It is not known whether SUPRAX is excreted in human milk. Consider discontinuing nursing temporarily during treatment with this drug.

**Pediatric Use:** Safety and effectiveness of SUPRAX in children aged less than 6 months have not been established.

The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension, was comparable to adult patients receiving tablets.

#### ADVERSE REACTIONS

Most adverse reactions observed in clinical trials were of a mild and transient nature. Five percent (5%) of patients in the US trials discontinued therapy because of drug-related adverse reactions. Commonly seen adverse reactions in US trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the bid or the qd regimen. Clinically mild gastrointestinal side effects occurred in 20% of all patients, moderate events occurred in 9% of all patients, and severe adverse reactions occurred in 2% of all patients. Individual event rates included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 4%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to adult patients receiving tablets.

Symptoms usually responded to symptomatic therapy or ceased when SUPRAX was discontinued.

Several patients developed severe diarrhea and/or documented pseudomembranous colitis, and a few required hospitalization.

The following adverse reactions have been reported following the use of SUPRAX. Incidence rates were less than 1 in 50 (less than 2%), except as noted above for gastrointestinal events.

**Gastrointestinal:** Diarrhea, loose stools, abdominal pain, dyspepsia, nausea, and vomiting. Several cases of documented pseudomembranous colitis were identified during the studies. The onset of pseudomembranous colitis symptoms may occur during or after therapy.

**Hypersensitivity Reactions:** Skin rashes, urticaria, drug fever, and pruritus.

**Hepatic:** Transient elevations in SGPT, SGOT, and alkaline phosphatase.

**Renal:** Transient elevations in BUN or creatinine.

**Central Nervous System:** Headaches or dizziness.

**Hemic and Lymphatic Systems:** Transient thrombocytopenia, leukopenia, and eosinophilia. Prolongation in prothrombin time was seen rarely.

**Other:** Genital pruritus, vaginitis, candidiasis.

The following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

**Adverse Reactions:** Allergic reactions including anaphylaxis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction, including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSE AND ADMINISTRATION** AND **OVERDOSAGE**). If seizures associated with drug therapy occur, discontinue drug. Administer anticonvulsant therapy if clinically indicated.

**Abnormal Laboratory Tests:** Positive direct Coombs test, elevated bilirubin, elevated LDH, pancytopenia, neutropenia, agranulocytosis.

#### OVERDOSAGE

Gastric lavage may be indicated, otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of SUPRAX did not differ from the profile seen in patients treated at the recommended doses.

\*\*Clinistest<sup>®</sup> and Clinistix<sup>®</sup> are registered trademarks of Ames Division, Miles Laboratories, Inc. Tes-Tape<sup>®</sup> is a registered trademark of Eli Lilly and Company.

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# CLINICAL STUDIES

## Surgery for Acquired Valvular Heart Disease: The San Pablo Heart Institute Experience

Manuel J. Martínez Colón  
Juan R. Vilaró Nelms

**Abstract:** Ninety nine patients underwent surgery for acquired diseases of the mitral and aortic valves between August 22, 1988 and August 21, 1990, of these, 64 procedures were done on the aortic valve and 35 procedures on the mitral valve. The early mortality for mitral valve surgery was 5.8% and late death occurred at a rate of 8.8%. As for the aortic valve surgery the operative mortality was zero and late death occurred at a rate of 3.4%. Thromboembolism occurred at a rate of 3.3% per patient year for patient undergoing mitral valve surgery and 6.3% per patient year for those undergoing aortic valve surgery. Valve thrombosis occurred at a rate of 6.6% per patient year for patients undergoing mitral valve surgery and zero for patients undergoing aortic valve surgery. Anticoagulation related bleeding occurred at a rate of 49% per patient year for patients undergoing mitral valve surgery and fatal bleeding at a rate of 3.3% per patient year. For those patients undergoing aortic valve surgery bleeding occurred at a rate of 25% per patient year and fatal bleeding occurred at a rate of 3.1%. This rate of bleeding appears high; and is due to poorly monitored anticoagulation.

The first attempt at correction of a valve lesion was done as early as the turn of the century by introducing the surgeon's finger within the heart and aorta. These procedures, however, had high complication rates and the patients it helped were few. Hoffnagle was the first to implant a prosthesis for relieve of aortic insufficiency implanting a ball and cage valve in the descending aorta. However it was not until the development of the heart and lung machine by Gibbons in 1953, that more precise surgery for valvular heart lesions could be attempted. The development and the implantation of the Starr Edwards prosthesis in 1969 is the crucial development that gave the cardiac surgeon an effective tool to relieve these ailments.<sup>1</sup>

Between August 1988 and August 1990 we performed 99 valve procedures at the San Pablo Heart Institute: 35 of them were performed on the mitral valve and 64 on the aortic valve. Six patients (1 mitral and 5 aortic) were lost to follow up therefore the report includes 93 patients or

94% follow up. Our results are presented herein including surgical mortality, late mortality and long term complication rates.

### Material and Methods

Nine hundred forty open heart operation were performed by us at the San Pablo Heart Institute between August 22, 1988 and August 22, 1990. Of these, 99 patients underwent procedures for acquired valvular heart disease, 6 patients were either lost to follow up or the hospital records contained insufficient data to be included in the study. Therefore, in 93 patients the records well felt to be complete; and accurate follow up could be obtained by telephone. Of these, 34 patients underwent procedures for acquired disease of the mitral valve and 59 procedures for acquired diseases for the aortic valve.

All procedures were performed under cardiopulmonary bypass with moderate systemic hypothermia, between (26°C and 28°C) and cold blood potassium cardioplegia for myocardial protection. Both vena cava were cannulated for venous return, in procedures on the mitral valve and single dual stage venous cannula was used for procedures on the aortic valve. Arterial return was provided into the root of the aorta for most patients, except those undergoing re-operations. For double valve procedures or combinations of aortic valve replacement and coronary artery bypass graft, cardioplegia was given by retro-perfusion of the coronary sinus.

All hospital records were scrutinized carefully and follow up was obtained through direct patient contact by phone and by reviewing office records in the follow up period. The data was collected and analyzed for early and late mortality, post-operative complications long term complications, and patient functional status. The patient profile for the 34 patient undergoing surgery for disease of the mitral valve is shown in Table I. The age range among these patients was between 16 and 76 years, and the average age was 54 years. Twenty one patients or 62% were female and 13 or 38% were male, showing a female predominance for patient with mitral disease. All patients with mitral lesions showed dyspnea on exertion as a predominant symptom. Forty one percent of the patients had history of congestive heart failure, 38% showed to be in atrial fibrillation, 29% had history of rheumatic fever, 32% had history of angina, 26% history of pulmonary edema, 18% had history of orthopnea, 2

Table I

Mitral Valve Surgery Patient Profile			
Age:	Range	16 to 76 Years	
Average		54 Years	%
Sex:	Male	13	38%
	Female	21	62%
Patients			
Dyspnea on exertion		34	100
Orthopnea		6	18
Angina		11	32
Congestive heart failure		14	41
Pulmonary edema		9	26
Atrial fibrillation		13	38
History of rheumatic fever		10	29
Endocarditis		2	6
Previous CVA		2	6
Reoperations		5	15
PRE OP NYHA Functional Class:			
I	0	0%	
II	6	20%	
III	23	77%	
IV	1	3%	
Cardiopulmonary Bypass Time			
Range	35 - 396	Minutes	
AVG	105.6	Minutes	
Aortic Clamp Time			
	Range 31 - 168	Minutes	
AVG	68.8	Minutes	

patients or 6% had history of endocarditis, and 6% of the patients showed history of previous cerebral vascular accident. Five patients, were re-operations. As for the pre-operative functional status no patient was found to be a Class I, 21% of the patients were Class II, 77% were in Class III and 3% were in Class IV, according to the classification by the New York Heart Association. Of the 34 patients with primary mitral diseases 20 had pure mitral stenosis, 8 had pure mitral regurgitation, 2 mitral stenosis and regurgitation, one patient had mitral stenosis and tricuspid regurgitation, one patient had mitral stenosis and aortic stenosis, and one patient mitral regurgitation and aortic regurgitation.

Twenty four patient were felt to be rheumatic disease in origin, 5 had degenerative diseases of the mitral Valve, 4 were felt to be ischemic mitral diseases and one had endocarditis. Therefore the operative experience included 19 mitral valve replacement, 6 mitral repair of which 5 were mitral commissurotomy, 2 mitral valve replacement and aortic valve replacement, 3 mitral valve replacement and tricuspid annuloplasty and 4 mitral valve replacement and coronary artery bypass grafts (Table I). Thus, 31 valves were implanted in 28 patients including one patient which had to undergo mitral re-replacement because of thrombosis of a St. Jude prosthesis. Of the valves used for replacement in primary mitral valve diseases 28 were mechanical prosthesis and all of them were St. Jude Medical, 3 patients had bioprosthesis implanted of which 2 were Carpentier Edwards type and

one was Metronix Intact. Four patients required annuloplasty rings of which 3 were placed in the Tricuspid position and one on the mitral.

The cardiopulmonary bypass time showed a range between 35 and 396 minutes with an average bypass time 105.6 minutes. The ischemic time showed a range between 31 and 168 minutes and average time of 68.8 minutes (Table I).

The profile for patients undergoing surgery for primary aortic disease is shown in Table II. The age range was between 30 and 80 years and the average 63.3. Thirty three or 26% were male and 26 or 44% were female. The most common symptom was shortness of breath which appeared in 97% of the patient, 42% showed angina as a primary symptom, 42% were known hypertensive, 34% were found to have diabetes mellitus, congestive heart failure was a predominant sign in 19%, previous myocardial infarction on 8%, 5% showed pulmonary edema, 3% had history of a previous stroke, 3% had history or were operated upon for endocarditis and re-operations was performed in 3% of the patients. The functional status according to the New York Heart Association Classification showed that 7% were Class IV, 59% were Class III, 34% were Class II and no patient was found to be a Class I.

The lesions for patient with a primary aortic valve disease showed that 37 or 62% had pure aortic stenosis, 15 or 25% had pure aortic insufficiency and or 12% of the patients had aortic stenosis and insufficiency. Since of the patients with primary aortic diseases underwent aortic

Table II

Aortic Valve Surgery Patient Profile			
Age:	Range 30-80	Years	
Average	63.3	Years	%
Sex:	Male	33	56%
	Female	36	44%
Numbers			
Shortness of breath		57	97
Angina		25	42
Hypertension		25	42
Diabetes mellitus		20	34
Congestive heart failure		11	19
Myocardial infarction		5	8
Pulmonary edema		3	5
Endocarditis		2	3
Previous stroke		2	3
Reoperation		2	3
PRE-OP NYHA Functional Class			
	Number	%	
I		0	
II	20	34	
III	35	59	
IV	4	7	
Pump Time:			
Range		71 - 212 Minutes	
AVG		109 Minutes	
Aortic Clamp Time:			
Range		51 - 138 Minutes	
AVG		75 Minutes	



valve repair, 57 aortic valves were implanted. Of these, mechanical prosthesis were used in 34 or 60% of which all of them were St. Jude Medical. Of the remaining 23 or 40%, 20 had a Carpentier Edwards and 3 had Medtronic Intact Bioprosthesis. Aortic valve replacement was performed in 42 patients or 71%; aortic valve replacement and coronary artery bypass graft was performed in 14 patients or 24%; one patient underwent aortic valve replacement coronary artery bypass graft and repair of a sinus Valsalva aneurysm which was infected; one patient had aortic valve repair, coronary artery bypass graft and resection of mycotic aneurysm of the ascending aorta, one patient underwent repair of the aortic valve in conjunction with the resection of a Type I aortic dissection (see Table III). For the patients undergoing surgery for aortic valve disease the cardiopulmonary bypass time range was between 71 and 212 minutes and the average 109 minutes. The aortic clamp time had a range between 51 and 138 minutes and the average time was 75 minutes (Table II).

Table III

Mitral Valve Operative Experience		Aortic Valve Operative Experience	
			#Patients
MVR	19	AVR	42
MR	6	AVR CABG	14
MVR, AVR	2	AVR, CABG, SV Aneurysm	1
MVR, TA	3	AV Repair Resection of	1
MVR, CABG	4	Aortic Aneurysm	
		AV Repair Resection of	1
		Aortic Dissection	
Total Procedures 34		Total	59
MVR : Mitral Valve Replacement MR : Mitral Repairs TA : Tricuspid Annuloplasty AVR : Aortic Valve Replacement CABG : Coronary Artery Bypass Graft SV : Sinus Valsalva AV : Aortic Valve			

## Results

The overall mortality for the entire series was 2 patients out of 93 patients undergoing valvular heart procedures or 2.2%; that of mitral related surgery was 5.8% and for aortic valve related surgery was zero. The late mortality was 5.4% or 5 patients out of 93 for the entire group. The late mortality for mitral valve surgery was 8.8% or 3 patients and that of aortic valve related surgery patients was 3.4% or 2 out of 59. The early deaths of patients who had undergone mitral valve surgery were due to myocardia failure in one patient and a cerebrovascular accident in another patient both of these patients were difficult re-operations, in one the patient had severe congestive heart failure and pulmonary edema at the time of surgery, the other one was a third time re-operation in whom the last surgery had been performed six weeks

previously at another institution, but she had developed a periprosthetic leak with severe hemolysis and congestive heart failure. The late deaths in patients who had undergone mitral valve surgery were to sudden death in one patient, intra-cranial hemorrhage, six weeks after the surgery, in another patient and thrombosis of a St. Jude mitral prosthesis 9 months after its implantation.

The late deaths for the group of patients that underwent aortic valve surgery was a late tamponade in an overly anticoagulated patient, and intra-cerebral hemorrhage in a patient that underwent aortic valve replacement for an infected sinus of valsalva aneurysm and endocarditis of the aortic valve.

The actuarial survival curve for patients who underwent mitral valve procedures is shown in Figure 1 and it shows that 85% of the patients were alive 25 months after surgery. The actuarial survival curve for patients who underwent aortic valve procedures is shown in Figure 2 and it shows that 96% of the patients were survivors at 25 months.

Figure 1

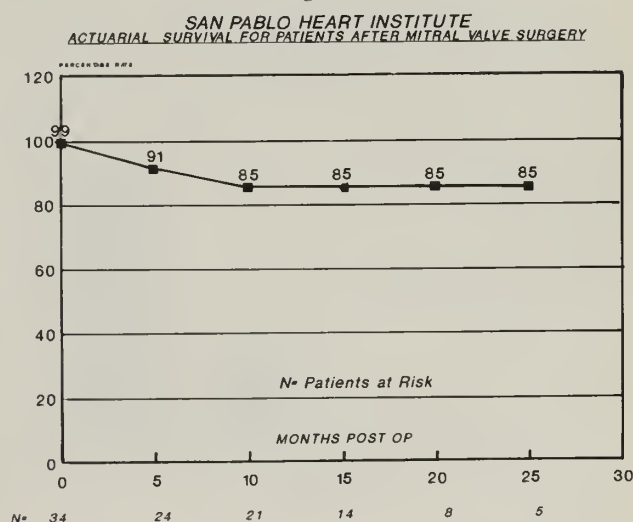
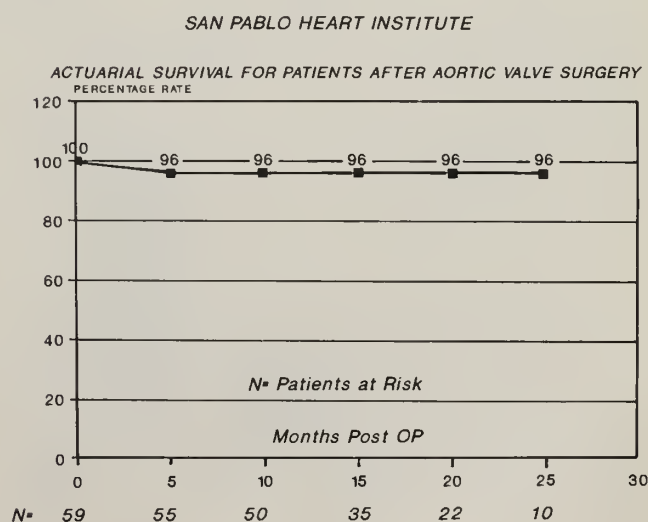


Figure 2



The post operative complications that occurred in patients who underwent mitral valve procedures is shown in Table IV. Twelve percent were found to have significant supraventricular arrhythmias, myocardial failure described as the need for inotropic support for over 24 hours was 12%; pleural effusions were found in 6% significant lobar atelectasis was found in 6%, ventricular arrhythmias was found in 6% and post operative hemorrhage requiring re-operations was found in 3%. For patients who underwent aortic valve procedures 20% had significant lobar atelectasis, 15% had supraventricular arrhythmias, 15% had pleural effusions, wound infection was found in 8.5%, pericardial effusions requiring drainage was found in 5%, ventricular arrhythmias was found in 5%, complete heart block 5%, pneumothorax 5%, respiratory failure requiring ventilation support over 48 hours 1.7%, gastrointestinal bleeding 1.7%, congestive heart failure 1.7%, cerebrovascular accidents 1.7% and post operate hemorrhage 1.7% (Table V).

Table IV

#### Mitral Valve Surgery Post Operative Complications

Complications	Number	Incidence
Supraventricular tachyarrhythmies	4	12%
Myocardial failure	4	12%
Pleural effusion	2	6%
Atelectasis	2	6%
Ventricular arrhythmias	2	6%
Post operative hemorrhage	1	3%

Table V

#### Aortic Valve Surgery Post Operative Complications

Complications	Number	Incidence
Atelectasis	12	20%
Supraventricular arrhythmia	9	25%
Pleural effusion	9	15%
Wound infection	5	8.5%
Pericardial effusion	3	5%
Ventricular arrhythmias	3	5%
Complete heart block	3	5%
Pneumothorax	2	5%
Respiratory failure	1	1.7%
Gastrointestinal bleeding	1	1.7%
Congestive heart failure	1	1.7%
Cerebrovascular accident	1	1.7%
Post operative hemorrhage	1	1.7%

Late complications for mitral valve surgery patients is shown in Table VI, thromboembolism occurred at a rate of 3.3% per patient year, valve thrombosis occurred at 6.6% per patient year and fatal valve thrombosis 3.3% per patient year, anticoagulant related bleeding was observed in 49% per patient year and in 3.3% per patient year it was fatal; valve failure was not observed as complication. As for patients who underwent aortic valve

surgery thromboembolism was found in 6.3% per patient year, (1.6% per patient year to the central nervous system), valve thrombosis was not observed, anticoagulant related bleeding was observed at a rate of 25% per patient year, and it was fatal 3.1% per patient year or 2 patients, life threatening bleeding described as episodes requiring admission to the hospital and/or blood transfusion occurred at 4.7% per patient year and valve failure was not observed (Table VII).

The anticoagulant related hemorrhage for those patients who underwent mitral valve surgery was due to hematuria in 9, oral cavity bleeding was in 2, soft tissue hematoma in 2 late tamponade in one patient and bleeding into the central nervous system in one patient

Table VI

#### Mitral Valve Surgery Long Term Complications

	Episodes	%/PT-YR
Thromboembolism	1	3.3
Valve thrombosis	2	6.6
Fatal	1	3.3
Bleeding	15	49
Fatal	1	3.3
Valve failure	0	0

Table VII

#### Aortic Valve Surgery Long Term Complications

	Episodes	%/PT-YEAR
Thromboembolism	4	6.3%
CNS	1	1.6%
Valve thrombosis	0	0
Bleeding	16	25
Fatal	2	3.1%
Life threatening	3	4.7%
Valve failure	0	0

for a total of 15 events. As for those patients undergoing aortic valve surgery hematuria was found in 7, late tamponade in 3, oral hemorrhage in 2, hemorrhage into the central nervous system in one, gastrointestinal bleeding in one, epistaxis in one and soft tissue hematoma in one. The actuarial complications free survival for patients undergoing mitral valve surgery is shown in Figure 3 and for those undergoing aortic valve surgery is shown in Figure 4. It shows that for those patient undergoing mitral valve surgery 56% were alive and free of complications at 25 months and those undergoing aortic valve surgery 58% were alive and free of complications.

The change in functional status according to the New York Heart Association Classification is shown in Figure 5 for patients undergoing mitral valve related surgery and Figure 6 for patients undergoing aortic valve related surgery. For those with mitral diseases we can see that



Figure 3

SAN PABLO HEART INSTITUTE  
MITRAL VALVE SURGERY PATIENT  
ACTUARIAL COMPLICATION FREE SURVIVAL

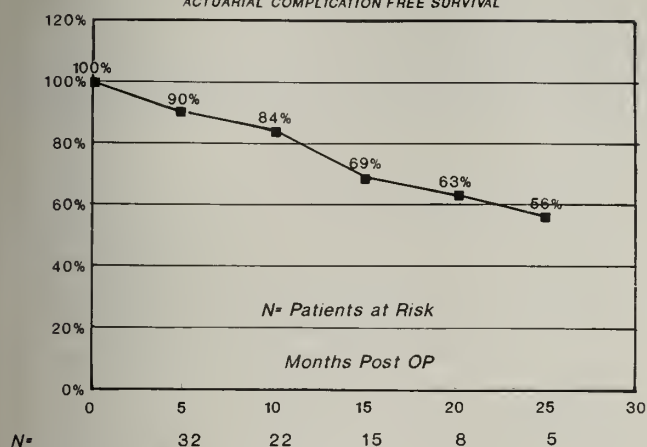


Figure 4

SAN PABLO HEART INSTITUTE  
ACTUARIAL COMPLICATION FREE SURVIVAL  
FOR PATIENTS AFTER AORTIC VALVE SURGERY

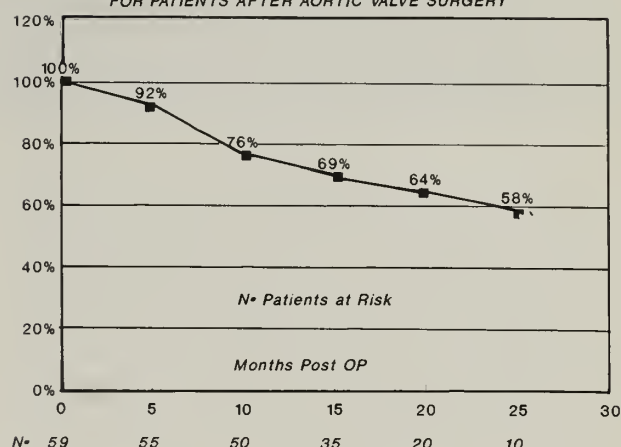


Figure 5  
San Pablo Heart Institute  
Functional Status for Patients  
After Mitral Valve Surgery

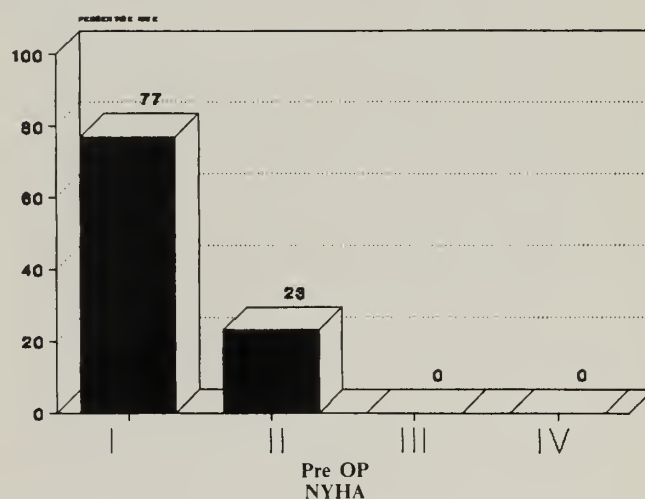
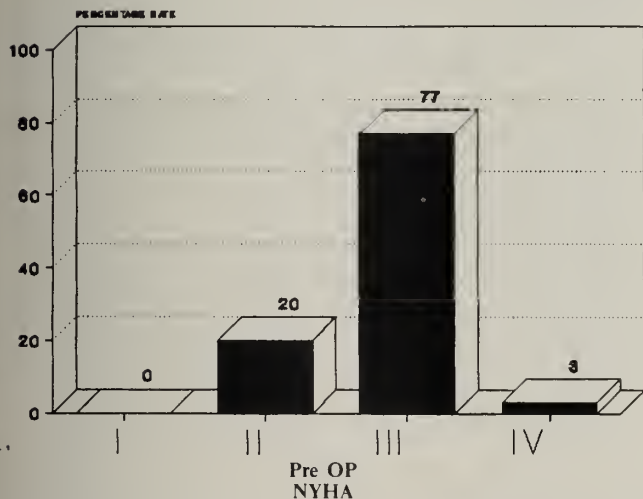
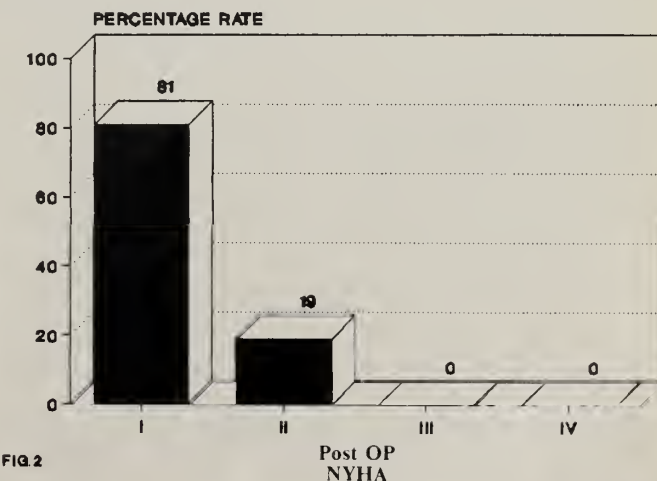
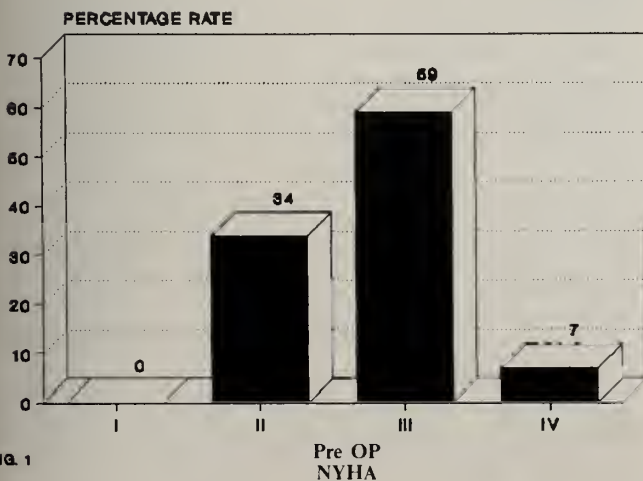


Figure 6  
San Pablo Heart Institute  
Functional Status for Patients  
After Aortic Valve Surgery



77% were classified as Class III pre-operatively, 20% Class II, and 3% Class IV; post-operatively all patients were in Class I or II with 77% of them classified as functional Class I or asymptomatic. For the patient who underwent aortic valve related surgery we can see that of 7% in class IV, 59% Class III and 34% Class II preoperatively; 81% were Class I and 19% Class II post operatively.

### Discussion

This study was designed to investigate peculiarities of our patient population rather than results with a particular valve prosthesis or surgical procedure, therefore patients were classified to a disease entity or valve pathology. Patients with multi-valvular involvement were grouped with mitral valve patients because their morbidity and mortality seems to be related to the mitral pathology or prosthesis rather than the combination. Our study population includes 93 patients for which all hospital records could be examined and a complete follow up could be obtained by either telephone communication and/or out patient records. The overall mortality for the series was 2.2% or 2 patients out of 93, for those patients undergoing primary mitral valve procedures it was 5.8% and for those patient who underwent aortic valve surgery it was zero, these number compare very favorable with those seen in the literature during this decade; reported series have shown a mortality range between 4.8% and 9.3% for mitral valve replacement and 2.9% to 8.3% for aortic valve replacement (2 to 10) this early mortality rate comes more encouraging when we consider that the 2 post operative death were patient in extremis, one patient died of myocardial failure after re-operation for a degenerated mitral valve prosthesis. This patient had refused surgery for 6 years and enter the hospital in pulmonary edema, severe congestive heart failure and anasarca, we performed mitral valve replacement as a last resource, her left ventricle could never develop adequate cardiac output post-operatively. The other death was on a patient operated for third time her, previous operation had been elsewhere six weeks previously from which she develop a severe periprosthetic mitral valve leak which cause her to be in congestive heart failure and severe hemolytic state, she died of intra-operative cerebrovascular accident of uncertain etiology.

Late death occurred in 3 patients following mitral valve surgery and in 2 after aortic valve surgery, for a combined incidence of 5.4% which is acceptable compared to that of the literature which has been reported between 4.5 and 12.1% (7 & 8).

The rate of thromboembolic events which in our series was 6.3% per patient year for aortic related surgery and 3.3% per patient year for mitral related surgery seems to be acceptable. Aris reported his incidence of thromboembolic episodes of 3.2% in patients undergoing mitral and aortic valve replacement with a Bjork-Shiley prosthesis (6); Storer reported in a similar series of patients an incidence of 1.7% per patient year with the St. Jude mechanical prosthesis (9). Thus, our incidence is acceptable and particularly encouraging since it has been known for years that most thromboembolic complications occur during the first two years after surgery, there-

fore as more patient years are accumulated in our series the thromboembolic rate is expected to fall.

We are concerned with the rate of anticoagulant-related bleeding which was 25% per patient year for patients undergoing aortic valve related surgery and 49% per patient year for patient undergoing mitral valve related surgery. When only fatal event are considered this incidence is 3.1% per patient year and 3.3% per patient year respectively. We are also seriously concerned with our two patients in whom St. Jude mechanical prosthesis in mitral position thrombosed, one of which was fatal. It is important to point out that in both cases inadequate anticoagulation could be singled as the cause. We, therefore, believe that our patient population is in need of aggressive awareness of the importance of adequate anticoagulation, we also believe that primary care physicians and patients alike should be made aware of the consequences of wide fluctuations in anticoagulation. A possible means by which this could be accomplished is the implementation of a coumadin clinic in our institution where careful and control monitoring of all patients on chronic anticoagulation could be done by experienced physicians.

Significant improvement in functional status could be observed in the surviving patients of our series, as for those undergoing mitral valve related surgery, all were found in New York Heart Association Class I or II post operatively. For those patient undergoing aortic valve related surgery all were found in Class I or II as well. Therefore surgery was effective in improving all patients functional status.

In summary in two years since valvular heart disease has been treated at the San Pablo Heart Institute we have accumulated experience with 93 patients, the early results for mortality and morbidity are acceptable. The incidence of anticoagulant related hemorrhage appears to be high; patient related factors primarily that of lack of knowledge of their disease seems to play very important role.

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# Foreign Bodies of the Esophagus the San Pablo Hospital Experience

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Pedro M. Mayol, MD\*\*

**Abstract:** Between 1978 and 1990, a total of 76 cases of esophageal foreign bodies were taken to the operating suite at San Pablo Hospital.

Of the 76 patients, 26 were in the pediatric age group, and 56 adults. Dysphagia and foreign body sensation were the predominant complaint. The radiographic study most frequently ordered was soft tissue neck x rays.

Coins were the most common foreign body in the pediatric group, while bones were the most frequent in the adult group. Rigid esophagoscopy was the predominant form of treatment in both groups. The majority of cases were performed by the Otolaryngologist-Head and Neck Surgeon. Several complications occurred and there was one death.

For the purpose of analysis and discussion the cases were divided into the pediatric age group and the adults.

Foreign bodies (F B) in the upper aerodigestive track are an important cause of morbidity and mortality today. In the United States each year about 3,000 people choke to death. Choking is the leading cause of accidental death in infants under twelve months of age<sup>1</sup>.

The event of a lodged foreign body in the upper aerodigestive track is a frightening and life threatening situation to most patients. Those who seek medical help have obviously survived the acute phase.

Since 500 B.C. removal of esophageal foreign body has been known. Aesop told of a crane placing his head in the mouth of a wolf to remove a bone lodged in the wolf's esophagus during rapid consumption of his prey<sup>2</sup>.

In this study the results of a retrospective review of the experience with foreign bodies of the esophagus at San Pablo Hospital are presented.

## Materials and Method

The medical records of all the patients with the diagnosis of foreign bodies of the esophagus between July 1978 and June 1990 at San Pablo Hospital were reviewed. Surgery was performed by Otolaryngologist-Head and Neck Surgeons, Thoracic Surgeons, Pediatric and General Gastroenterologists. A total of 80 cases were identified in the computerized registry of surgical procedures. Four cases were excluded from this report because their esophagoscopy was not intended for foreign body, but rather for esophageal obstruction secondary to distal esophageal strictures and in two other

cases dislodgement of the foreign body occurred before going to the operating suite.

The remaining 76 patients records were reviewed for esophageal foreign body. No carcinoma of the esophagus was found, and no patient was treated medically.

For the purpose of analysis the case population was divided in two groups. Group A, the pediatric age group for ages 1 to 18 years of age. Group B, the adult population ages 19 to 90 years of age.

## Results

### Group A

There were 26 patients in the pediatric age group. There were 16 males and 10 females. The ages were from 1 to 13 years of age. The mean age was 4.3 years. Twenty-three (23) patients were treated by Otolaryngologist-Head and Neck Surgeons. The remaining 3 patients were treated by a Pediatric Gastroenterologist. Eighty eight percent (88%) of the patients had rigid esophagoscopy for removal of the foreign body; 12% were removed via flexible fiberoptic pediatric gastroscope. Eighty percent (80%) of the patients were admitted through the emergency room and 38% of the patients had been seen at another hospital.

Eleven (11) patients reported dysphagia, 10 foreign body sensation, 10 cough, 5 shortness of breath, 4 drooling, 1 vomiting and 5 had no symptoms. Eighty eight percent (88%) had symptoms for less than twenty four hours, 8% more than forty eight hours and 4% for more than two weeks. Seventy six percent (76%) had soft tissue of neck x-rays, 65% chest x-rays and 7% barium swallow esophagogram.

In 16 patients their foreign body was found at the level of the cricopharyngeal muscle, in 7 patients at the mid esophagus and in 3 patients at the stomach. Coins were the most frequent foreign body found. Table I summarizes the f.b. removed.

Table 1

Group A foreign bodies removed from esophagus in children between 1978-1990 at San Pablo Hospital

Coins	18
Pin	2
Fishbone	1
Thumbtack	1
Diaper Clip	1
Jack	1
Vegetable	1

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One patient received pre-operative antibiotic while eight patients were given antibiotics post operative. Eighty four percent (84%) of the patients were discharged

from the hospital after 24 hours observation. Complications were observed in two patients. One had an asthmatic episode and one had mild bleeding. No blood transfusion was required. There were no deaths.

### Group B

There were 50 patients in the adult group, 20 males and 30 females. The ages range from 19 to 90 years of age. The mean age was 50.7 years. Forty one (41) patients were treated by Otolaryngologist Head and Neck Surgeons, 4 Thoracic Surgeons, 2 Gastroenterologist and 3 in combination by the Otolaryngologist and Gastroenterologist. Ninety percent (90%) of the patients were admitted through the emergency room and 26% had been evaluated at another institution. One patient was an in-patient being treated for a medical condition.

Foreign body sensation was the most common complaint in 49 patients, 36 reported dysphagia, 8 odynophagia, 7 cough, 5 chest and neck pain, 3 shortness of breath, 3 drooling, 2 respiratory distress and one vomiting.

Thirty six (36) patients had symptoms for less than twenty four hours, 11 patients had symptoms for two days. Two patients each for three and four days. One patient had symptoms for eight days and 1 patient had symptoms for over two months.

The diagnostic study most frequently ordered was a soft tissue of neck x-ray in 48 patients, 30 chest x-ray, 24 barium swallow esophagogram, 1 gastrograffin esophagogram and 1 C.T. Scan. Forty five (45) patients underwent rigid esophagoscopy, 2 flexible fiberoptic gastroscopy, 1 bronchoscopy and 3 patients had a combined procedure of rigid and flexible fiberoptic esophagoscopy.

Forty (40) foreign bodies were removed, 4 foreign bodies identified at the stomach and in 6 patients the foreign body was not found. Twentyeight (28) f.b. were found at the level of the cricopharyngeus muscle, 8 at the mid esophagus and 3 at the distal esophagus.

Chicken bones were the most common f.b. removed. Table II summarize the f.b. removed. Six (6) patients received antibiotic pre-operative and twenty (20) patients post-operative, cephalosporins being the antibiotics most widely used. Thirty seven (37) patients were discharged on post-op day one, 2 patients each by post-op day two, three, and four. One patient discharge on post-op day five and two on day eight. The average hospital stay was 1.6 days.

Table 2

Group B foreign bodies removed from esophagus in adults between 1978-1990 at San Pablo Hospital	
Chicken bone	17
Fishbone	9
Meat	6
Pork chop bone	4
Dental prosthesis	3
Fried pork skin	1

Complications occurred pre and post operative. Two patients had pre-operative complications. One had pneumomediastinum presumed secondary to a penetrating foreign body associated with a vigorous Heimlich maneuver. The other patient aspirated barium contrast. Post operative two patients had persistent dysphagia. One required flexible fiberoptic esophagoscopy and was found with severe reflux esophagitis. There was one patient with persistent chest pain, 1 ARDS (Adult Respiratory Distress Syndrome), 1 COPD (Chronic Obstructive Pulmonary Disease), 1 Diabetes Mellitus, and one respiratory failure.

One death occurred in an elderly patient who upon barium swallow esophagogram had total esophageal obstruction causing the patient to aspirate barium. Post operative the patient developed respiratory failure, ARDS and died. Fig. 1



Figure 1. Chest x-ray elderly patient who aspirated barium.

### Discussion

Frequently physicians will go to their library seeking additional current information regarding the diagnosis and treatment of a medical condition. Upon request of additional information in the management of esophageal f.b., it was a surprise that few reports originated in the otolaryngologic literature. The literature is full with articles on reports of complications and new modalities of treatment. Furthermore, many textbooks use as references a series of cases reported in the 1950's<sup>3, 4</sup> and 1960's<sup>5</sup>. Since that time a few things have changed and some should be mentioned.

Once the patient arrives to the hospital, the acute episode has passed. The patient will have most of the time less distressing symptoms. Once the patient is evaluated, and it is determined that he is no longer in danger, a thorough history and physical examination should be performed including an indirect laryngoscopy. A careful review of the history is warranted, in particular to details and vague symptoms. It is vital to establish the type of f.b. since sharp objects may cause perforation. Asymptomatic patients may be misleading, specially in children. Five



patients in the pediatric group had no symptoms other than the parents suspicion of an ingested f.b.

Negative radiologic studies may be misleading as well. One patient had a choking episode with a chicken bone. A Heimlich manouever was performed. The patient was evaluated at another institution, had radiographic studies performed with negative yield. The patient came to the hospital 24 hours after with a vague complaint of f.b. sensation and chest discomfort. Radiographic studies included soft tissue of neck, chest x-ray, gastrograffin barium swallow esophagogram and C.T. Scan of the mediastinum with negative results. Consulted physicians felt that the chest complaint was related to costochondritis, secondary to a vigorous Heimlich manouever. A diagnostic esophagoscopy was declined by the patient. Forty-eight hours later, the patient returned with the same complaints. New radiographic studies revealed a small pneumomediastinum and a C.T. Scan could not exclude a f.b. A flexible fiberoptic esophagoscopy was performed and a foreign body is identified in the mild esophagus but could not be removed. Finally the patient was taken to the operating room where a large chicken bone was removed.

Despite this case, radiographic studies are a valuable source of information. Sixty percent (60%) of the adult patients in this series had chest x-rays. Chest x-rays should be performed in all patients with suspected foreign body especially if one suspects a complication related to a sharp object. In this series chest x-rays were helpful determining complications in two patients. One had barium aspiration and the other a pneumomediastinum. In those patients with drooling or suspicion of total esophageal obstruction, precautions should be undertaken with contrast studies. CT Scan may be a source of valuable information in those cases of suspected perforation.

The type of f.b. ingested were similar to other series reported. In children coins are the most common while in adults, meat bones are the most frequent<sup>6</sup>. The cervical esophagus is the level where most f.b. will be found<sup>7</sup>. Comparing this series to others reported series regarding symptoms and duration of impaction, the results are similar<sup>8</sup>, with dysphagia and f.b. sensation being the most common complaint. The time elapsed since the impaction of the f.b. and receiving medical attention in the majority of the patients in both groups, was 24 hours or less.

In the acute phase of choking, the Heimlich manouever, properly performed, may be a life saving manouever. The treatment of esophageal foreign body can be medical or surgical. The author advocates the surgical treatment with rigid esophagoscopy because it is a safe and controlled technique with years of proven success. In this report 93% of the patients were treated surgically by rigid esophagoscopy. Since the introduction of the flexible fiberoptic endoscope there have been reports of endoscopists removing foreign bodies.<sup>9, 10</sup> Non endoscopic technique for f.b. extraction has been the use of Foley catheters.<sup>11</sup>

Medical regimens include the use of papain<sup>12</sup>, glucagon<sup>13</sup> and diazepam<sup>6</sup>, but serious complications have been reported. Two deaths occurred in a series using

papain secondary to esophageal perforation.<sup>14</sup>

Untreated and unrecognized esophageal foreign bodies may migrate into the surrounding soft tissue and cause severe and dreadful complications. In a report by Remsen and Et. Al. 1983<sup>15</sup> of Unusual Presentation of Penetrating Foreign Bodies of the Upper Aerodigestive track, the overall mortality associated with penetrating foreign body was 45%. This report was a review of the world literature of penetrating foreign body with 321 cases reported between 1818 and 1983. The greatest mortality was in the pre antibiotic era. In another report by Nandi and Org 1978,<sup>8</sup> presenting a series of 2,394 patients treated for esophageal foreign body, there were 24 cases of serious complications of neck abscess and esophageal perforation with 3 deaths.

Medical progress over the past 30 years has been astonishing. The development of new antibiotics, the Heimlich manouever, flexible fiberoptic scopes, the development of new diagnostic modalities, (such as CT Scan, MRI), Intensive Care Units, parental nutrition, cardiovascular and respiratory care, and the overall improved patient care, has resulted in a significant reduction in patients morbidity and mortality in the management of esophageal foreign bodies.

**Resumen:** Entre el 1978 y 1990 un total de 76 casos de cuerpo extraño en el esófago fueron llevados a Sala de Operaciones en el Hospital San Pablo.

Cincuenta (50) pacientes eran adultos y veintiséis (26) pacientes eran de la edad pediátrica. Disfagia y sensación de cuerpo extraño fue la queja predominante. La radiografía lateral de cuello fue el estudio radiográfico más utilizado. Monedas fue el cuerpo extraño mayormente removido en los niños mientras que el hueso de pollo fue el más abundante en los adultos. La esofagoscopia rígida fue el método de remoción de cuerpo extraño más frecuentemente utilizado en ambos grupos. Los Otorinolaringólogos-Cirujanos de Cabeza y Cuello trataron la mayoría de los casos. Hubo varias complicaciones y una mortalidad.

Para el propósito de análisis y discusión, los casos fueron divididos en dos grupos. Los de la edad pediátrica y los adultos.

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# The Use of Audiocassette Recordings for Patient Education

Miguel V. Buxeda, MD\*

Patient education is an ideal strived for by all concerned physicians, nurses, pharmacists and other health care professionals and their patients. Patient education can improve patient satisfaction and compliance, have a positive influence on the doctor-patient relationship and decrease the likelihood of malpractice litigation.<sup>1, 5</sup>

But, as all practicing physicians know, patient education can be time consuming and many times ineffective.<sup>6, 11</sup>

The use of patient education audiocassettes can be an effective way to solve this problem.

There is a scarcity of published research in this area. Baskerville, P. et al. reported on their use of audiocassette recordings for the education of 119 patients prior to inguinal surgery.<sup>12</sup> In their study, they reported that 99% of the patients had access to a cassette player, that patients listened to the tape from one to twenty times (mean 3.3 times), and that 36% of the patients listened to the tape more than twice.

They also reported that 75% of the patients listened to the tape with their spouses and a significant minority (15%) listened in the company of friends and neighbors. Ninety-eight percent of the patients found the tape beneficial and 98% of the patients suggested that similar tapes should be made available for other common medical conditions.

Jenkinson et al. compared the effects of a self-management booklet and an audiocassette recording for the education of patients with asthma.<sup>13</sup> Their results showed that patients given the tape learned more than the patients given the self-instructional booklet. Thirty-one percent of the patients found the book useful, whereas 62% found the tape very useful.

A study was designed to test the effectiveness of a patient education tape in teaching and motivating hypertensive patients to take steps that could help them control their high blood pressure.

## Methods

An audiocassette recording was prepared in the Spanish language entitled "How to Control Your Hypertension."

The recording was 50 minutes long and was divided into six parts. At the start and end of the recording, and

between each of the parts, a musical theme was heard.

The first part of the recording was entitled "Why do you need to control your blood pressure?". The second part was entitled "What is hypertension?". The third part was entitled "What causes hypertension?". The fourth part was entitled "Measures to lower your blood pressure." The fifth part was entitled "Your use of medications."

The recording was accompanied by a specially designed full color instruction booklet which fit inside the plastic jacket of the audiocassette recording. The booklet contained illustrations, summaries and a table of the most commonly prescribed antihypertension medications.

Hypertensive patients waiting to be seen at the San Pablo Hospital Ambulatory Care Center were asked to participate in a patient education study. All volunteers were required to be over 18 years old, and to have a telephone number where they could be reached and an audiocassette player available to them.

They were also told that the recording on "How to Control Your Hypertension" would be provided free of charge, but that we needed them to return to the hospital in approximately one week in order to find out their opinion of the cassette and what they learned from hearing it.

Data was collected of the participants' age, sex, education, income, occupation, telephone number and home address. Participants were also questioned as to whether they had received education on hypertension from their physician or nurse, and whether they had read pamphlets or books on hypertension previous to the study.

An oral examination was then administered to the participants, consisting of 50 statements, to which the subjects were asked to respond as being "True" or "False," or simply state that they didn't know. The participants were encouraged not to guess, and to reply that they didn't know if they really didn't know or were very unsure of the answer.

After the Pre-Test, each patient volunteer was given a copy of the audiocassette presentation. They were instructed that they could hear it as many times as they wanted to, whenever and wherever they wanted to, alone or in the company of others. They were told that they didn't have to listen to the tape if they didn't want to.

An appointment was made for the subjects to return to the hospital, approximately one week after the initial encounter. When the participants returned to the hospital, a series of questions were asked regarding their use of the audiocassette recording. Participants were also asked if there were any commentaries they wished to make. A post-test was then performed orally, identical to the pre-test.

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## Results

Fifty-seven (57) hypertensive patients volunteered to participate in the study during the week of June 25 to June 29, 1990. Forty (40) or 70.2% returned to the hospital to complete the post interventional interview and take the post-test.

Of the seventeen (17) participants who did not return to the hospital, nine (9) were contacted by telephone. Of these nine, seven (7) stated that they had heard the recording, but had been unable to return to the hospital. Two (2) stated that they had not listened to the tape.

The seven subjects who had heard the tape but had not returned to the hospital agreed to answer the oral post-intervention interview and take the oral post-test over the telephone. Statistical analysis showed that their answers did not deviate from those of the subjects who returned to the hospital, and they were included in the study.

All post intervention interviews and post-tests were performed within 10 days of the participants' having received the tape.

The age of the 47 patients who took the post-test ranged from 32 to 81 years. Fourteen or 29.8% were under 49 years of age, 26 or 55.3% were between 50 and 64 years of age, and 7 or 14.9% were 65 years of age or over. Thirty-four (34) or 72.4% were female; thirteen (13) or 27.6% were male.

There was a wide distribution in the self-reported years of school completed. Two (2) participants had never gone to school and were completely illiterate (4.25%). Fifteen had received between 1 and 8 years of education (31.9%). Nineteen (19) subjects had completed between 9 and 12 years of school (40.9%), and 11 subjects had over 13 years of formal education (23.4%).

The subjects' self-reported yearly income also showed a wide range. Two subjects (4.2%) stated they were unemployed at the time. Seventeen (17) or 36.2% reported a yearly income of under \$7,500. Fifteen (15) or 31.9% reported a yearly income between \$7,500 and \$15,000 and 13 subjects reported an income of over \$15,000 a year. In this higher income group, the average income was \$25,970.00.

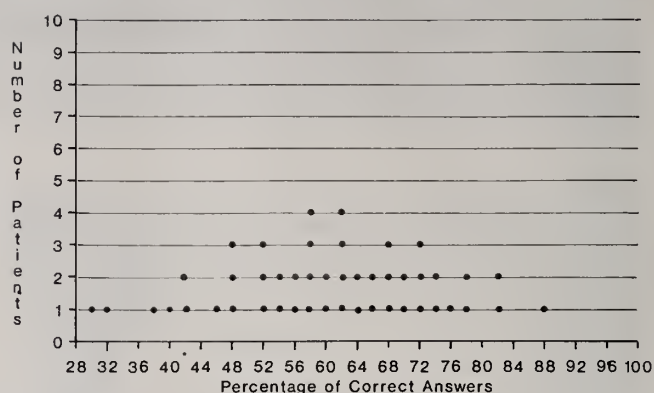
Only 14% of the participants stated that their doctor or nurse had given them any education on hypertension. Most stated that their doctors had only given them instructions on how to take their medications. Thirty-four (34) or 72.3% stated that they had read pamphlets or books on hypertension.

The participants listened to the recording a mean 2.75 times with a minimum of one and a maximum of ten. Seven (7) subjects (14.9%) listened to it once. Eighteen (18) subjects (38.3%) listened to it twice and 22 subjects (46.8%) listened to it 3 or more times. There was no statistically significant difference in the number of times males or females listened to the recording.

Eighteen subjects (38.8%) listened to the recording in their cars, thirty-nine listened in their homes (83%) and one subject reported listening to it at work. Fifteen (31.9%) reported listening to it alone, thirty (63.8%) reported listening with family members, one (2.1%) reported listening to it with a friend and another (2.1%) with fellow workers.

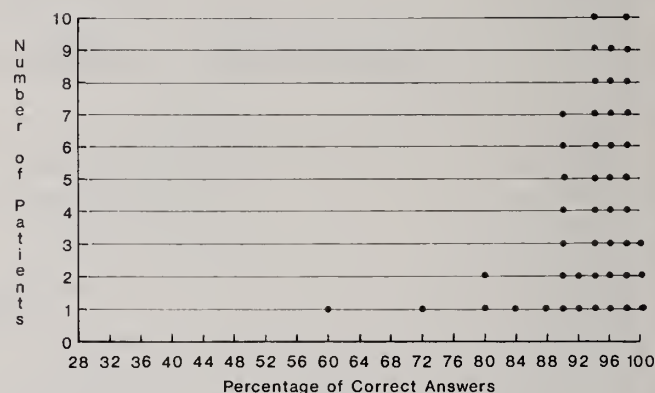
Graph 1 shows the distribution of correct answers on

## Pre Test Scores of Knowledge of Hypertension in 47 Hypertensive Patients



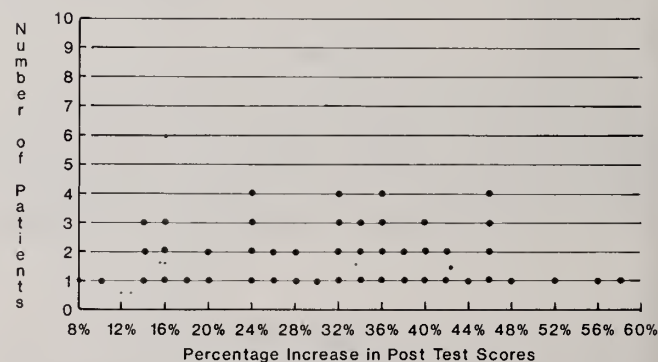
Graph 1

## Post Test Scores of Knowledge of Hypertension in 47 Hypertensive Patients



Graph 2

## Percentage Increase in Post Test Scores of 47 Patients Who Listened To An Audio Cassette Presentation on Hypertension



Graph 3



the pretest and Graph 2 shows the distribution of correct answers on the post-test. The mean in the pre-test was 60.47% with a minimum of 30% and a maximum of 88%. The mean in the post-test was 92.15% with a minimum of 60% and a maximum of 100%. Graph 3 illustrates the percentage increase in post-test scores.

A t-test was performed to compare the average scores in the pre-test and the post-test and the difference was found to be statistically significant ( $p = 0.05$ ).

There were no statistically significant differences in the pre-test or post-test scores between subjects with different levels of education. However, there was a tendency for participants with higher levels of education to score higher in the post-test. (See Table 1).

Table 1

Pre and Post Test Scores According to Educational Level of 47 Hypertensive Patients

	Pre	Post
All	60.46	92.14
1 - 8	62.53	90.66
9 - 12	58.52	93.73
13+	64	96.18

The two subjects who had never attended school and were completely illiterate scored a mean 44% on the pre-test and a mean 66% on the post-test.

There were no statistically significant differences in pre and post-test scores according to sex (Table 2) or age (Table 3), although there was a tendency for younger subjects to score higher in the post-test.

Table 2

Pre and Post Test Scores According to Sex of 47 Hypertensive Patients

	Pre	Post
All	60.46	92.14
Male	58.40	92.73
Female	61.43	91.87

Table 3

Pre and Post Test Scores According to Age of 47 Hypertensive Patients

	Pre	Post
All	60.46	92.14
49	55.85	94.42
50 - 64	62.84	92.42
65+	60.85	86.57

There was also a tendency for subjects to score higher on the post-test depending on how many times they had heard the recording (Table 4).

Table 4

Post Test Scores According to Number of Times the Recording was Heard

	Post
All	92.14
1 Time	84.28
2 Times	92.72
3 Times or More	94.18

When asked their opinion of the cassette presentation, all participants stated that they could understand it; 66% stated that they could understand "all or almost all" of it and 34% replied they could understand "most of it". All participants stated they thought the recording had helped them understand hypertension; 80.9% replied it had helped them "a lot."

All participants stated that they thought the recording had helped them understand what they could do to control their hypertension, 85.1% replied it had helped them "a lot."

Ninety-eight percent of participants thought the recording had helped them understand high blood pressure medications, 85.1% replied it had helped them "a lot." All the respondents stated that the recording had motivated them to control their blood pressure; 89.4% of the respondents felt "a lot more motivated" to control their blood pressure and 95.7% felt they were going to feel "a lot more comfortable" talking to their physician after having heard it. All stated they would recommend the recording to family and friends.

Fifty-one percent (51%) of the participants made commentaries specifically stating how the recording had increased their knowledge of hypertension, cleared up doubts and helped them understand medical terms better.

Seventeen percent (17%) of the participants made commentaries which reflected their increased motivation with regards to blood pressure control. Statements were made by 10.6% of the subjects reflecting the fact that the recording had made them realize how important it was to control their blood pressure.

Another 10.6% of the participants made statements that reflected their interaction with family members, friends and co-workers while listening to the tape and 17% gave notice of specific behavior changes such as going on a diet, using less salt and checking the sodium content of cans before buying them.

## Discussion

The data in this study shows that substantial increments in knowledge can be obtained by patients when they hear audiocassette recordings, regardless of their age, sex, or level of education. These increments could be obtained, most likely, because the medium used was the spoken language instead of the written one. Also, the use of simple, nontechnical terms, liberal repetition, and motivational techniques could have a lot to do with the results obtained.

Of the patients who heard the audiocassette 89.4% were a lot more motivated to control their high blood pressure, and 95.4% said they thought they would feel "a lot more comfortable" talking to their physicians.

The patients of behavior of these patients and the character of their relationship with their physicians will be followed in order to determine whether the reported increases in knowledge and in motivation translate themselves into healthier and more assertive ways of dealing with their hypertension.

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V CONGRESO PUERTORRIQUEÑO DE CARDIOLOGIA**

**APRIL 18-21, 1991**

## CALL FOR ABSTRACTS

The Scientific Program Committee  
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# REVIEW ARTICLE

## The National Cholesterol Education Program: Guidelines and Commentaries

Alfonso Zerbi, MD

**Summary:** There is overwhelming evidence that atherosclerosis is caused by elevated cholesterol levels and that the process can be prevented, arrested, and even reversed by altering the cholesterol fractions. The National Cholesterol Education program established guidelines for the management of hypercholesterolemia. Classification of cholesterol values are: Desirable 200 mg./dl, Borderline high 200-239 mg./dl high risk 240mg./dl and above. Total cholesterol is used for case finding and screening, but LDL cholesterol is the key index for decisions requiring treatment. Classification of LDL levels is as follows: High risk 160mg./dl and over, Borderline 130 to 159 mg./dl, Acceptable 130mg./dl and below. Secondary and familial disorders should be identified. Dietary therapy is the cornerstone of cholesterol reducing interventions. -Steps one and two diets are described, with limitations of saturated fats to 10% of total calories and cholesterol to 300 mg./daily in step one; step two diet limits saturated fats to 7% of total calories - and cholesterol to 200 mg./daily. Pharmacotherapy is based on 5 groups of hypolipemic agents:

- A- Resins (cholestiramine and colestipol)
- B- Nicotinic acid
- C- Probucol
- D- Fibric acids (gemfibrozil)
- E- Reductase inhibitors (lovastatin).

Some areas of criticism and controversies regarding the guidelines are discussed and identified.

Coronary artery disease is the most common cause of death in the Western world and produces an extremely heavy toll in premature loss of life and direct and indirect economic cost. High plasma cholesterol levels, hypertension and smoking *have been* established as the most important risk factors for the development of premature coronary artery disease.

The current focus on the cholesterol issue arises from the fact that there is now overwhelming evidence that atherosclerosis is caused by elevated cholesterol levels. Numerous animal, epidemiologic and genetic studies have shown that altering circulating cholesterol levels can arrest, prevent, and even reverse the progression of coro-

nary atherosclerosis<sup>1, 2, 3, 4</sup>. Elevated levels of low density lipoprotein cholesterol (LDL) and decreased levels of high density lipoprotein cholesterol (HDL) are related epidemiologically to accelerated atherosclerosis<sup>12-6</sup>. Two landmark intervention studies: The Lipid Research Clinic Primary Prevention Trial<sup>1</sup> and The Helsinki Heart Study<sup>3</sup> provided the necessary data conclusively showing that cholesterol lowering is associated with reductions in the incidence and mortality of coronary artery disease.

The understanding of the role of various lipoproteins in the atherosclerotic process has been greatly advanced by the recognition of the Nobel prize winners, Drs. Brown and Goldstein of LDL mediated endocytosis<sup>10</sup> and by the role of modified LDL in atherosclerosis described by Drs. Carew and Steinberg<sup>9</sup>.

The public health issues raised by the accumulated evidence are enormous, and in response, the National Heart, Lung and Blood Institute organized the National Cholesterol Education Program in 1987, with the cosponsorship of the American Heart Association and other health organizations. The Expert Panel on High Blood Cholesterol in Adults published its report in 1988<sup>5</sup>, providing a series of guidelines offering the practitioners a framework for the therapeutic interventions and management of hypercholesterolemia.

### National Cholesterol Education Program Guidelines - Screening:

The panel recommends that all adults 20 years of age and older should have their cholesterol levels checked, and if normal (200 mgs./dl) or less should be rechecked in five years.

### Initial Classification Requiring Treatment:

The total cholesterol value is utilized as initial case finding and classification, but the LDL cholesterol fraction level is the key index in the decisions requiring treatment.

Classification according to total cholesterol values is as follows:

- Desirable ..... (200 mgs./dl)
- Borderline high ..... (200 mgs./dl to 239/dl)
- High risk ..... (240 mgs/dl and above)

All adults should be evaluated for the presence of other Coronary artery disease risk factors which are:

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1. Male sex.
2. Family history of premature coronary artery disease (angina, myocardial infarction or sudden death below age 55, in a parent or sibling).
3. Cigarette smoking (10 cigarettes or more/day).
4. Hypertension.
5. Low HDL cholesterol (35 mgs/dl or less) confirmed by repeated measurements.
6. Diabetes mellitus.
7. History of definite cerebrovascular occlusive disease or peripheral vascular disease.
8. Severe obesity ( $\geq 30\%$  overweight)

Patients with desirable plasma levels of total cholesterol (200 mgs./dl) or below should be educated in a "prudent diet" and risk reduction, and be re-checked for total cholesterol in five years.

Patients with borderline plasma cholesterol levels should have their cholesterol level re-analyzed, and the average of two or more samples used for decision making. The panel recommends that lipoprotein analysis be performed in patients with borderline high plasma cholesterol with established coronary artery disease or who have two risk factors for CAD and in all patients with high plasma cholesterol (240 mgs./dl) and above. For lipoprotein analysis 12 hour fasting is necessary to obtain total cholesterol, triglycerides and HDL cholesterol levels. The LDL cholesterol value is then derived from the following formula:  $LDL\ chol. = total\ cholesterol - HDL\ cholesterol - triglycerides/5$ .

The calculation is reliable as long as the triglycerides levels are below 400 mgs./dl.

The classification according to the LDL levels is as follows:

- High risk -- 160 mgs./dl. and above
- Bordeline -- 130 to 159 mgs./dl
- Acceptable -- 130 mgs./dl and below

For follow up purposes the total cholesterol levels can be utilized, considering a rough equivalent of total cholesterol of 200 mgs/dl to 130 mgs/dl of LDL cholesterol and 240 mgs/dl of total cholesterol to 160 mgs/dl of LDL.

Plasma triglycerides levels may be associated with CAD, particularly in women above age 50 years. Normal triglyceride levels were defined as 250 mgs/dl or below, borderline high between 250 and 500 mgs/dl and high above 500 mg dl. Treatment of hypertriglyceridemia is not contemplated in the guidelines except for those with exceptionally high values because of the risk of pancreatitis.

### Secondary Factors and Familial Disorders:

A clinical evaluation is required to determine whether the patient has a primary lipid disorder or if it is secondary to another disease or drug use. Secondary causes of high risk LDL cholesterol levels are:

1. Hypothyroidism
2. Nephrotic syndrome
3. Diabetes mellitus
4. Obstructive liver disease
5. Drugs, particularly progestins and anabolic steroids.

If a secondary cause is identified, the appropriate therapy is that of the underlying disease entity.

Several genetically determined lipid disorders are associated to atherosclerotic disease and occur with the following frequencies:

Condition	Frequency
Familial hypercholesterolemia .....	1/500
Familial combined hyperlipidemia .....	1/100
Familial dysbetalipoproteinemia .....	1/5000

Familial hypercholesterolemia is the result of a defect in the gene decoding for the LDL receptor. Consequently, LDL receptors resulting from the defective gene will be either absent or malfunctioning resulting in high LDL levels in plasma. Familial combined hyperlipidemia is characterized by increases in one or more lipoprotein species in members of a single family. Some family members have elevated VLDL alone; others have only increased LDL; and still others have high levels of both. Familial dysbetalipoproteinemia is marked by the accumulation of intermediate density lipoprotein, a precursor of LDL.

For those individuals with confirmed total cholesterol greater than 240 mgs/dl, lipoprotein profile should be obtained on immediate relatives.

### Treatment Decisions:

Decisions as to therapy are made according to the LDL cholesterol levels and the presence of other risk factors. Those with high LDL cholesterol or borderline high LDL and 2 other risk factors or established CAD, cholesterol reducing therapy is in order after establishing that the cholesterol level is not secondary to other disease state or drug therapy. The LDL level, however, should be confirmed by repeated examinations 1 to 8 weeks apart before initiating any pharmacologic treatment program.

The goals of any therapeutic intervention are to reduce LDL cholesterol levels to/or below 160 mgs/dl in those with no CAD or 2 risk factors and to 130 mgs/dl or below in those with 2 coronary disease risk factors or established CAD.

### Diet Therapy:

Dietary therapy is the cornerstone of cholesterol reducing therapeutic interventions, and should be continued even if pharmacotherapy is later required. The American Heart Association and the National Cholesterol Education Program has described two diets -Steps one and two- to reduce cholesterol levels. Step one diet, restricts the intake of total fats to 30% of the total caloric intake, with limitation of the saturated fats to 10% of the total calories, 10% of the caloric intake by monounsaturated, and the other 10% by polyunsaturated fats. The total daily cholesterol ingestion is limited to 300 mgs. or less. The diet also indicates increase in the intake of soluble fiber, and adjusting total caloric intake according to ideal body weight. If the therapeutic goal is not achieved in a period of 4-6 weeks, the step two diet is initiated, which entertains a further limitation of the saturated fats to 7% of the total caloric intake, and further reduction of the cholesterol intake to 200 mgs. per day. A six month period of intensive dietary therapy is recommended before consideration of the use of drugs.

If the total cholesterol is adequately controlled, LDL cholesterol levels should then be measured to confirm desirable levels. Long term follow up with quarterly



monitoring the first year and at 6 mos. intervals thereafter is recommended. Other risk factors modifications, as smoking cessation, weight reduction and an exercise program should be utilized concomitantly. Pharmacologic therapy can be considered before the six month period in high risk groups, when LDL levels are markedly elevated to 225 mgs/dl or above and in those with diagnosed coronary disease.

### Pharmacologic Therapy

Pharmacotherapy is utilized as an adjunct to diet, not as a replacement. Drug therapy is initiated in adults after the initial non-pharmacologic intervention period when the LDL cholesterol level is 190 mgs/dl or above in those with no coronary disease and fewer than two risk factors, and at a LDL chol. level of 160 mgs/dl in patients with CAD or two risk factors. The goal of therapy is to reduce LDL levels to or below 160 mgs/dl in the lower risk group and to 130 mgs/dl or below in the high risk group.

There are five groups of medications that are utilized in the treatment of the hyperlipedemic states. A short discussion of the salient features of each group of drugs follows. The practitioner should familiarize himself with each medication before prescribing from an adequate source of information (PDR, etc.).

#### A- Bile Acids Sequestrants - (Resins)

Two resins are currently utilized: cholestiramine (Questran) and colestipol (Colestid). Equivalent doses of the two drugs are 4 Gms. of cholestiramine to 5 Gms. of colestipol. Both are supplied in individual dose packets and in less expensive bulk cans.

The resins are non absorbable compounds that interrupt the enterohepatic circulation of bile acids in the intestine, increasing their fecal excretion. This effect results in an enhanced elimination of cholesterol, increased conversion of cholesterol to bile acids and decreased hepatic cholesterol content, producing an increased number of LDL receptors and increased clearance of LDL from the plasma. The dosage of cholestiramine averages 16 Gms. daily, divided in two doses, given with meals.

The resins primarily lower LDL cholesterol, they also produce a modest increase in HDL cholesterol and are indicated in the treatment of familial and non familial hypercholesterolemia and familial combined hyperlipidemia. Patients with moderate increases of the triglyceride levels can have a modest increase in their triglycerides with these drugs, but the resins are contraindicated in endogenous hypertriglyceridemia (type IV) and dysbetalipoproteinemia (type III) because marked increases in triglycerides and cholesterol levels may occur. Side effects are primarily gastrointestinal, most frequently constipation, abdominal pain, flatulence and nausea. They can also interfere with the absorption of simultaneously administered drugs such as warfarin, thiazides, digoxin, thyroid hormones, beta blockers and gemfibrozil.

#### B- Nicotinic Acid:

Nicotinic acid, a B Vitamin, was utilized in the Coronary Drug Project and its effectiveness was confirmed in reducing the risk of coronary heart disease, and

in long term follow up reduction of total mortality.<sup>4</sup> In therapeutic doses, it decreases total cholesterol, LDL cholesterol and triglyceride levels, while increasing HDL cholesterol levels. It is the least expensive of the hypolipedemic agents. Tolerance is enhanced by the use of sustained release preparations, but they are also more expensive.

Nicotinic acid is an inhibitor of lipoprotein synthesis and decreases the secretion of VLDL, a precursor of LDL, from the liver. It is useful in the management of familial hypercholesterolemia, polygenic hypercholesterolemia, dysbetalipoproteinemia, familial combined hyperlipidemia and hypertriglyceridemia.

Side effects to nicotinic acid in therapeutic doses are frequent and multiple. The major side effect is flushing, which is prostaglandin mediated and can be decreased by pretreatment with aspirin, by taking the medication with meals and by the use of the sustained release forms. Upper gastrointestinal tract symptoms are frequent; it can activate duodenal ulcer disease. Elevation of serum uric acid levels, with precipitation of gout and abnormal liver function tests, particularly alkaline phosphatase and liver enzymes are noted. Decreased glucose tolerance is occasionally seen in patients with type II diabetes.

Therapy should be initiated at low dosage levels of 250 mgs daily in divided doses, and gradually increased to a daily total of 1 to 1.5 gms. The lipid profile is then rechecked and the dosage can be increased, if tolerated, to a total of 3 gms if necessary. Side effects increase markedly above that dosage level.

#### C- Probucol

The main effect of probucol (Lorelco) is in lowering the LDL cholesterol levels. It does not affect triglycerides levels and decreases HDL cholesterol levels by as much as 20% to 25%. Probucol is marketed in 250 and 500 mgs. tablets, and the usual dosage is 500 mgs. twice a day.

Potential benefit is suggested by decreases in xanthoma size in patients with familial hypercholesterolemia. There is experimental evidence that probucol has other effects, including a potent antioxidant effect that decreases the amount of LDL that accumulates in macrophages and other tissues.<sup>11</sup> Because of its HDL lowering effect, and absence to date of clinical trials in long term follow up to prevent CAD, it is not considered a drug of first choice. Its most frequent side effects are gastrointestinal, including loose stools, diarrhea, and abdominal discomfort. Prolongation of the QT interval in the electrocardiogram might occur, and it should not be used in patients with prolonged QT intervals. Tolerance is generally good.

#### D- Gemfibrozil (Fibric Acids)

Gemfibrozil (Lopid) was the drug used in the Helsinki Heart Study<sup>3</sup> and showed, in the five year randomized trial, a 34% decrease in fatal and non fatal myocardial infarctions, associated with a decrease of only 9% of LDL and a 10% increase in HDL. The subgroup showing the greatest benefit were those with elevated total cholesterol and triglyceride levels and low HDL levels.

This drug is available in 300 mgs. capsules and 600 mgs. tablets, the usual dosage being 600 mgs. twice a day. It is primarily effective in lowering VLDL and triglyceride levels and increasing HDL levels. Its effect on LDL is variable. Gemfibrozil is indicated primarily in the treatment of hypertriglyceridemia especially when associated with low HDL levels, type III hyperlipidemia (dysbetalipoproteinemia) and type II B hyperlipidemia. Most patients tolerate the drug well; side effects being mainly gastrointestinal, but it shows no adverse effects on either uric acid or glucose levels. Myalgias with increases in CPK has been reported, but they are infrequent.

#### E- Lovastatin (Reductase inhibitors)

Lovastatin (Mevacor) is the only 3-OH-3-methylglutaryl coenzyme A reductase inhibitor currently available, but others of this group of drugs should be marketed shortly. They are competitive inhibitors of the rate-limiting step in cholesterol biosynthesis. The resulting decrease in hepatic cholesterol content produces an increase in the number of LDL receptors, and increased uptake of LDL from the plasma. The decrease in LDL is dose dependent, and reductions of 25% to 45% are noted. HDL cholesterol show modest increases of appx. 8%, and a 15% to 25% decrease in the triglyceride levels is also observed. Therapy is usually initiated with a single 20 mgs. tablet with the evening meal and may be gradually increased to a maximum of 80 mgs. daily. The usual dose range is from 20 to 40 mgs daily. It is effective in familial and non familial hypercholesterolemia, type III dysbetalipoproteinemia and familial combined hyperlipidemia.

The drug is well tolerated, with discontinuation of the drug in only 1% of patients in short clinical trials and in 3% in long term ones. Hepatotoxicity, manifested by transaminase levels three times normal occurs in 1.9% of treated patients, occurring from 3 to 15 months after initiation of therapy.

It is recommended that liver enzymes be monitored at 4 to 6 weeks intervals during the first 15 months of treatment, and that the drug be discontinued if marked increases (3 fold) in liver enzymes occur. The effect is totally reversible once the medication is discontinued. Myositis, including myalgia and elevated creatin kinase levels occur rarely (0.5%) when the drug is given alone.

Myopathy, including rhabdomyolysis with or without acute renal failure has been reported when used in combination with cyclosporine (30% incidence), with gemfibrozil (5%), with nicotinic acid (2%) and occasionally with erythromycin. Cataract formation has been observed with higher doses of lovastatin in dogs, but no cases has been documented in humans. Recommendations approved by the Food and Drug Administration include baseline and yearly follow up slit lamp examinations.

Lovastatin is a potent, well tolerated cholesterol lowering drug offering advantages of ease of administration, tolerability, and no other drug interactions.

Hypercholesterolemia is a chronic illness, and the patient may require prolonged, sometimes lifetime treatment, so the practitioner must consider patient tolerance, compliance, cost, as well as efficacy when

selecting a pharmacologic agent. If the goals of treatment are not achieved, combination of drugs should be considered, and finally, consultation and referral to a lipid expert if therapy is unsuccessful.

#### Comments and Discussion:

The recommendations of the Expert Panel have defined the minimal steps that a practitioner is expected to take in managing patients with hypercholesterolemia. Since their publications, they have produced a major impact, increased public and physician awareness of the problem, and in general, gained widespread acceptance.

They have also produced some criticism and concern.

The usefulness of the guidelines depends in the accuracy of the lipid measurements by the laboratory. The Lipid Standardization Panel of the National Heart, Lung and Blood Institute's National Cholesterol Education Program has recommended that cholesterol measuring methods should be traceable to a reference standard. Each laboratory should at least establish the relationship between its methods and reference methodology. A good laboratory should be able to measure total plasma cholesterol with an accuracy that averages  $\pm 3\%$  and a coefficient of variation of 3%.<sup>14</sup> The variability of VLDL and LDL measurements will be greater, with similar difficulties in the HDL analysis, making the value of a single measurement of HDL to assess cardiovascular risk somewhat limited.<sup>14</sup>

The report has been most vigorously criticized for its emphasis on LDL cholesterol values, and lack of emphasis on triglycerides and HDL cholesterol.<sup>7</sup> Some persons with total cholesterol in the 200 mgs. range will have HDL levels of less than 35 mgs/dl and will, therefore, be at risk of coronary artery disease and are not identified by the recommended screening of total cholesterol.<sup>7</sup> Furthermore, as many as 70% of patients with total cholesterol levels of 200 mgs/dl that also have CAD have HDL levels of  $<40$  mgs/dl<sup>6</sup> and the guidelines do not provide for the treatment of this group of individuals.

In the PROCAM<sup>12</sup> and Framingham<sup>6</sup> studies HDL levels and total chol/HDL ratios were found to be excellent predictors of risk for CAD. A significant group of patients, especially pre-menopausal females, with high total cholesterol, high LDL levels above 160 mgs/dl, but with also high levels of HDL, and with a Total cholesterol/HDL ratio below 4.5, that according to the current epidemiologic data from Framingham are at low risk, would be candidates for pharmacotherapy according to the guidelines. This could represent overtreatment to a low risk group, that according to Dr. Castelli<sup>13</sup> should only require diet counseling.

The response to the guidelines will lead to increased public expectations for cholesterol-related counseling and the need for greater physician proficiency on dietary intervention and in the use of lipid-lowering drugs. The most important aspect, however, is that the widespread application of the guidelines promises a significant reduction in the incidence of CAD among our population.



**Resumen:** Existe hoy día abundante evidencia de que la arteriosclerosis es causada por elevación de los niveles sanguíneos de colesterol y de que este proceso puede evitarse, detenerse y hasta revertirse bajando los niveles séricos de colesterol. El Programa Nacional de Educación del Colesterol establece guías para el manejo de la hipercolesterolemia. Los valores de colesterol se clasifican como sigue: Deseables 200 mg/dl; fronterizo alta 200-239mg./dl -alto riesgo- 240 mg./dl o más. El colesterol total se utiliza para búsqueda de casos, pero los niveles de colesterol de baja densidad (LDL) representan el índice para las decisiones referentes a tratamiento. La clasificación del LDL es como sigue: Alto riesgo -160 mg./dl-más; fronterizo 130-159 mg./dl; aceptable 130 mg./dl. Las formas secundarias y familiares de hipercolesterolemia se deben identificar.

El tratamiento dietético representa el puntal de las intervenciones terapéuticas para reducir los niveles de colesterol. Dos dietas -paso uno y dos se describen limitando las grasas saturadas a 10% del total de calorías y el colesterol a 300 mg./diario en el paso 1, el paso 2 limita las grasas saturadas al 7% del total de calorías y el colesterol a 200 mg./diario. La farmacoterapia se basa en 5 grupos de agentes hypolipidémicos.

A Resinas (colestiramina y colestipol).

B Acido nicotínico.

C Probucol.

D Acidos fibricos (gemfibrozil).

E Inhibidores de la reductasa (lovastatina).

Algunas áreas de crítica y controversia referente a las guías se discuten y se identifican.

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**Warning:** Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

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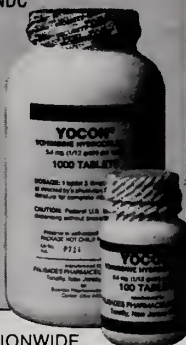
**Dosage and Administration:** Experimental dosage reported in treatment of erectile impotence.<sup>1,3,4</sup> 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.<sup>3</sup>

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1. Data on file, G.D. Searle & Co.
2. 1988 Joint National Committee: The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1988;148:1023-1038.

### BRIEF SUMMARY

**Contraindications:** Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

**Warnings:** Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

**Precautions:** Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration.

Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

**Adverse Reactions:** Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°, 2°, 3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, increased urination, spotty menstruation, impotence.

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# CASE REPORT

## Pneumopericardium Complicating Bronchial Asthma in a 4 Year Old Child

Samuel Vázquez Agosto, MD  
Ivette Rico, MD  
José E. Sifontes, MD  
Pedro M. Mayol, MD

**P**neumothorax and pneumomediastinum are not infrequent complications of bronchial asthma in children. Pneumopericardium, on the other hand, is a very rare occurrence in a child with bronchial asthma, particularly so in one who is not sufficiently ill to require intubation or mechanical ventilation.

**Patient Report** - A 4-year-old white female with history of bronchial asthma had never been hospitalized and was being treated with a beta-adrenergic by oral route, only as needed. She was doing well until the day of admission when she developed a dry cough and respiratory difficulty. After a trial with bronchodilators at the emergency room, she was admitted to the hospital because of lack improvement. Her respiratory rate was 36/min, blood pressure 120/80 mmHg, and temperature 37°C (oral). She was acutely ill, appeared alert, in moderate distress and was well hydrated. She had nasal flaring, intercostal, subcostal and suprasternal retractions, decreased breath sounds throughout both lung fields and bilateral expiratory and inspiratory fine wheezing. No crackles were heard.

While breathing room air arterial blood pH was 7.35, PaCO<sub>2</sub> 47 mmHg, PaO<sub>2</sub> 63 mmHg, bicarbonate 26 mmol/L (26 mEq/L), base excess .7 and oxygen saturation 91 percent. While breathing 40 percent oxygen (Venturi mask) pH was 7.4, PaCO<sub>2</sub> 40 mmHg, PaO<sub>2</sub> 126 mmHg, bicarbonate 27 mmol/L (27 mEq/L), base excess 3.2 and oxygen saturation 98.6 percent.

The white-cell blood count was  $18.0 \times 10^9/L$  (18,000/mm<sup>3</sup>) with 0.96 (96 percent) neutrophils and 0.04 (4 percent) lymphocytes - Hemoglobin was 136 g/L (13.6 g/dL). The serum sodium was 135 mmol/L (135 mEq/L), potassium 3.7 mmol/L (3.7 mEq/L), chloride 105 mmol/L (105 mEq/L) and CO<sub>2</sub> 25 mmol/L (25 mEq/L).

Theophylline level while receiving aminophylline 0.9 mg per Kg per hour by the intravenous route was 15.4 micrograms per ml. Chest roentgenogram on admission as shown in figure 1 revealed no air leaks. Treatment consistend of oxygen by mask, aminophylline continuous



Figure 1. Admission Chest X-Ray

infusion and corticosteroids by the intravenous route in addition to an inhaled beta adrenergic agent.

During the night the patient had increased cough and sudden onset of chest pain. At this time, her heart rate was 130 per minute, respiratory rate 38 per minute, blood pressure 120/80 mmHg and temperature 36.8°C (oral). She was alert, well oriented, dyspneic and in moderate distress. Nasal flaring, supraclavicular and subcutaneous emphysema were noted. Auscultation of the lung revealed bilateral expiratory and inspiratory wheezing. There were no murmurs, no S3 nor S4 sounds, no cyanosis and no edema. Good symmetrical pulses were palpated in the extremities. Arterial blood pH was 7.37, PaCO<sub>2</sub> 20 mmHg, PaO<sub>2</sub> 137 mmHg, bicarbonate 12 mmol/L (12.0 mEq/L), base excess 10.7 and oxygen saturation 98.7 percent. Chest roentgenogram was repeated and as shown in figure 2, revealed pneumopericardium.

Treatment was unchanged and improvement was noted during the next few days. There was no cardiovascular compromise at any time. Chest roentgenogram 72 hours after the onset of pneumopericardium showed resolution of the problem (Fig. 3). The patient was discharged home 7 days after admission doing well.

### Comment

Although reports are numerous with respect to pneumopericardium (PNPD) in neonates with pulmo-



Figure 2. Pneumopericardium



Figure 3. Resolution pneumopericardium

nary problems<sup>1, 2</sup> or adults with trauma, it is a rare complication in a 4-year-old patient with status asthmaticus who is not intubated nor receiving mechanical ventilation. In a series of 515 pediatric asthma admissions, roentgenographic abnormalities of the chest were found in 22 percent of the patients.<sup>3</sup> Fifteen percent over 10 years of age and none below the age of 2 years.

In another review by Brooks and coworkers of children hospitalized for asthma, pneumonia or pneumothorax was reported in 5.5% of the patients.<sup>4</sup> In none of the above articles nor in others involving asthma in children, has pneumopericardium been reported.<sup>5</sup>

The mechanisms whereby PNPD can occur, have been postulated by Macklin to involve bronchospasm, mucosal edema and inspissation of secretions which cause air trapping and overdistention resulting in stretching of alveoli.<sup>6</sup> Supporting structures such as the pulmonary arteries, pulmonary veins and alveolar septa, have limited elasticity and as alveolar overdistention progresses, shearing forces develop by exaggerated respiratory efforts, rupturing the marginal alveolar bases. The escaping air dissects along perivascular sheaths toward the hilum, aided by the lengthening and shortening movements of the blood vessels during respiration. Having reached the mediastinum, air may escape to form pneumomediastinum which may be asymptomatic or

may lead to frank air block and death. It seems reasonable to postulate that air dissecting centripetally along the pulmonary arteries and veins could dissect through the pericardial reflection on these vessels and result in pneumopericardium. Histological preparations<sup>2</sup> have been made to demonstrate the site of reflection of parietal pericardium onto visceral pericardium near the ostia of the pulmonary veins. These revealed a site of potential weakness at the reflection.

Toledo<sup>7</sup> has divided PNPD according to different etiologies: a) Iatrogenic: Instances in neonates or infants circumstantially related to positive pressure ventilation; thoracentesis, paracentesis; post-sternal bone marrow aspiration; post-transthoracic gastroesophageal procedures with subsequent gastropericardial fistula formation; post-cauterization of esophageal webs with subsequent esophagopericardial fistula formation.

b) Infections: Pericarditis; extension of a septic process from adjoining organs (tuberculosis, empyema).

c) Fistula formation between the pericardium and an adjacent air containing organ.

d) Trauma

The most common presenting symptoms<sup>7, 8</sup> are dyspnea and precordial pain, when present. A "metallic rub" or a sound like "rice krispies" synchronous with cardiac impulse can be present on auscultation (Hamman's sign) being more pronounced during systole.

It is not always easy to differentiate PNPD from pneumothorax or pneumomediastinum by anteroposterior and lateral chest roentgenograms.

Decubitus films can help in establishing the diagnosis through the following findings:<sup>9, 10</sup>

a) pericardial gas will be seen to shift within the pericardial sac.

b) mediastinal air will not move in the short time interval between films.

c) pneumothorax air will rise to the lateral margin of the pleural cavity.

A reduction in cardiac size of 30% or more<sup>11</sup> can cause marked hemodynamic changes consisting of decreased atrial and ventricular filling, decreased stroke volume and cardiac output, hypotension, increased central venous pressure and pulsus paradoxus. However, treatment for the most part frequently involves nothing more than watchful waiting. In severe cases, immediate pericardiectomy may be indicated. In specific instances other modalities may be indicated such as appropriate antibiotics and specific surgical procedures aimed at the correction of the underlying causes of fistula formation.

While literature is abundant with respect to pneumomediastinum and subcutaneous emphysema complicating asthma,<sup>5, 12</sup> reports are rare with respect to PNPD complicating asthma. Pneumopericardium in the pediatric age group is reported in neonates in respirators due to respiratory distress and in children and adolescents due to trauma. Report of case of a 4-year-old female patient with status asthmaticus who, without having being exposed to intubation or mechanical ventilation, developed pneumopericardium along with subcutaneous emphysema is presented. Although not common, one must be aware of the possibility of this complication since it could be an immediate life threatening event requiring urgent intervention.



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# PROGRESS REPORT

## Transrectal Prostatic Ultrasound Peripheral Hypoechoic Lesions: A Progress Report

José Anzalotta, MD

**Summary:** From July 1, 1989 to June 30, 1990, 432 cases of transrectal prostatic ultrasound were done at San Pablo Hospital. Low density lesions were found in 85 patients in the peripheral zone. Twenty of these 85 cases proved to be malignant for an incidence of 23%. Our experience from January 1, 1988 to June 1989 was published previously.<sup>1</sup> At that time, of a total of 486 cases, 72 patients showed low density lesion in the peripheral zone. Thirty-seven of these proved malignant for an incidence of 51.4%. To our original publication<sup>1</sup> we are adding our recent 85 cases with 20 malignant lesions for a total of 157 cases of low density lesions and a total of 57 malignant lesions. We now have an average incidence of 36.3% malignancies in low density peripheral lesions.

Prostate cancer is the third leading cancer in men over the age of 55 according to the American Cancer Society. Over 100,000 new cases of prostate cancer will occur in the U.S. in 1990 and close to 30,000 patients will die of the disease.<sup>1</sup> The internal structure of the prostate can be evaluated with the use of transrectal ultrasound using a short focus 7 MHZ transrectal transducer.<sup>2</sup> The lesions found in the transrectal ultrasound of the prostate which are suspicious of carcinoma can then be evaluated by needle biopsy using transrectal ultrasound for localization.

### Materials and Methods

From July 1, 1989 to June 30, 1990, 432 cases of transrectal prostatic ultrasound were done at Centro de Imágenes at San Pablo Hospital. This 12 month period yield and average of 36 cases per month. These patients were referred by the urologist and attending physician from Bayamón and nearby communities because of abnormal digital exam and/or increased serum prostatic specific antigen (PSA). Patient's age ranged from 40 to 82 years. The size of lesions in the peripheral zone ranged from 0.4 cm to 1.8 cm.

### Results

Of a total of 432 studies (Transrectal Prostatic Ultrasonogram), 85 cases showed low density lesions in



Figure: 1A - Transverse plane  
Low density lesion peripheral zone.

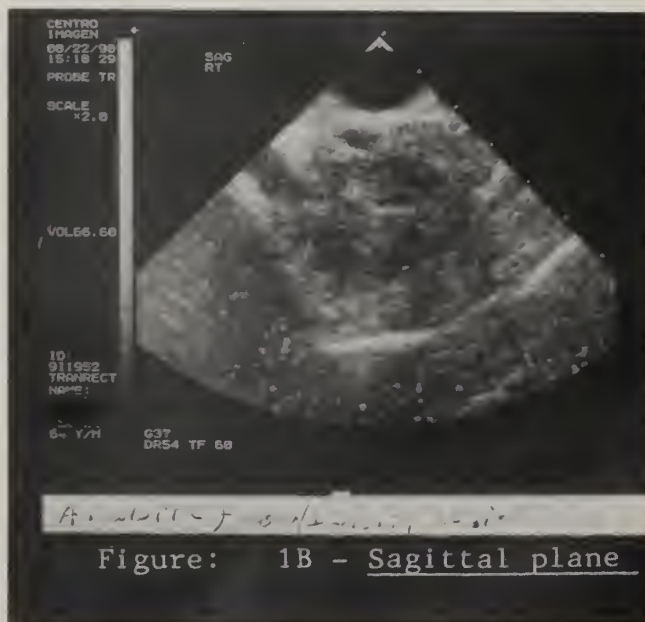


Figure: 1B - Sagittal plane

From the Department of Radiology, San Pablo Medical Center, Bayamón, Puerto Rico

the peripheral zone, which were biopsied by different staff urologists with transrectal prostatic ultrasound guidance using the automatic Swedish biopsy instrument (Bioptic), with an 18 gauge needle. Twenty cases of the 85 low density lesions proved to be malignant for an incidence of malignancy of 23%. Adding the previously reported cases<sup>1</sup> of 72 low density lesions out of which group, 32 proved to be malignant, we have a total of 157 low density lesions 57 of which were malignant giving us an average incidence of 36.3% malignancies in low density lesions at the peripheral zone in the group of 918 patients we have studied with transrectal prostatic ultrasonography between January 1, 1988 and June 30, 1990.

### Discussion

The peripherally located, hypoechoic lesion is the most characteristic appearance of prostatic cancer in the transrectal prostatic ultrasound.<sup>3</sup> Prostatitis, muscles around the ejaculatory ducts, large veins near the capsule and cysts can also present as hypoechoic lesions. These lesions can be accurately diagnosed using transrectal prostatic needle biopsy guided by ultrasound. The procedure can be done on an outpatient basis.

In addition to transrectal prostatic ultrasound, earlier work has shown the usefulness of serum prostatic specific antigen (PSA) for evaluation of patient with prostatic adenocarcinoma.<sup>4</sup> Unfortunately PSA is not prostatic cancer specific since it is elevated in benign prostatic hypertrophy and in prostatitis. PSA is helpful in the identification of individuals who may have prostatic cancer or other prostatic pathology and in treatment monitoring of prostate cancer patients.

**Resumen:** Durante el período del 1ro. de julio de 1989 al 30 de junio de 1990, se hicieron 432 casos de ultrasonido endorectal prostático en el Hospital San Pablo. Lesiones de baja densidad fueron demostrados en 85 pacientes. De éstos, 20 casos resultaron ser malignos para una incidencia de 23%. Los casos de ultrasonido endorectal prostáticos de San Pablo durante el periodo del 1ro. de enero de 1988 al 30 de junio de 1989 fueron reportados previamente (2). En ese reporte de un total de 486 casos estudiados, 72 mostraron lesiones de baja densidad en la zona periferal de la próstata. Treinta y siete fueron malignos para una incidencia de 51.4%. Sumando nuestros casos recientes en este reporte de 85 casos de lesiones de baja densidad y 20 lesiones malignas arrojan una suma total de 157 lesiones de baja densidad con un total de 57 lesiones malignas para una incidencia promedio de malignidad de 36.3%.

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# ARTICULOS ESPECIALES

## El Health Care Quality Improvement Act de 1986

Milton L. Cruz, JD, LL.M.\*

**Resumen:** Se discute en forma general los requisitos más importantes de la ley federal titulada "Health Care Quality Improvement Act of 1986" desde el punto de vista de las instituciones hospitalarias en Puerto Rico. Se discute además los aspectos de suspensión de privilegios, obtención de inmunidad y la obligación de solicitar y de reportar información al Banco Nacional de Data bajo la mencionada ley federal.

El propósito de este artículo<sup>1</sup> es el exponer y analizar en forma general los requisitos más importantes de la ley Health Care Quality Improvement Act del 1986, según enmendada,<sup>2</sup> desde el punto de vista de los hospitales.

El estatuto contiene dos subcapítulos, a saber 1) promoción de actividades sobre revisión de profesionales y 2) sobre reportar información. Básicamente, el Congreso de los Estados Unidos de Norte América llegó a unas conclusiones fundamentales sobre los problemas de impericia médica y calidad de los servicios médicos. Estas conclusiones están expuestas en la ley de la siguiente manera:

The Congress finds the following:

- (1) The increasing occurrence of medical malpractice and the need to improve the quality of medical care have become nationwide problems that warrant greater efforts than those that can be undertaken by any individual State.
- (2) There is a national need to restrict the ability of incompetent physicians to move from State to State without disclosure or discovery of the physicians' previous damaging or incompetent performance.
- (3) This nationwide problem can be remedied through effective professional peer review.
- (4) The threat of private money damage liability under Federal laws, including treble damage liability under Federal antitrust law, unreasonably discourages physicians from participating in effective professional peer review.
- (5) There is an overriding national need to provide incentive and protection for physicians engaging in effective professional peer review.<sup>3</sup>

Basado en lo anterior, el Congreso adopta el estatuto Health Care Quality Improvement Act del 1986.

### I. Suspensión de Privilegios Médicos en Puerto Rico

La adopción del Health Care Quality Improvement Act puede ser de gran beneficio para Puerto Rico. En Puerto Rico, al igual que en los Estados Unidos, se puede dar el caso que una vez un hospital determina el suspender los privilegios médicos a un galeno el mismo demande al hospital y/o a los miembros del comité que tomó la decisión alegando que se violaron sus derechos.

En Puerto Rico el Tribunal Supremo solamente ha tenido la oportunidad de discutir la teoría de suspensión de privilegios médicos en hospitales privados o de la comunidad en el caso de *Hernández v. Asoc. Hosp. del Maestro*.<sup>4</sup> De esta opinión se desprenden las siguientes guías generales en cuanto a este tema, a saber:

1. Los médicos afectados tienen que agotar los procedimientos internos del hospital antes de acudir a los tribunales.
  2. Los tribunales darán gran deferencia a las normas procesales de los Reglamentos de un hospital si las mismas cumplen con las garantías mínimas del debido proceso de ley.
  3. Las normas adoptadas por un hospital serán respetadas por los tribunales a menos que sean muy vagas, subjetivas o caprichosas.
  4. Un hospital privado puede suspender, retirar o limitar privilegios de un médico, pero no de forma irrazonable, caprichosa o arbitraria.
  5. Médicos excluidos en forma irrazonable de la Facultad Médica pueden ser repuestos.
  6. El médico tiene derecho a una audiencia para presentar prueba a menos que "su continúa presencia en el hospital constituyera una seria e inmediata amenaza."
- Lo anterior nos indica que en Puerto Rico los tribunales dan gran deferencia a las determinaciones de los hospitales y el contenido de sus Reglamentos a menos que a) "...la reglamentación no satisfaga los requisitos mínimos del debido proceso de ley..." y b) "sus determinaciones sustantivas sean arbitrarias, caprichosas o irrazonables."<sup>5</sup>

El cumplimiento por las instituciones de la sección de promoción de revisión de actividades profesionales de la ley federal ayudará en gran medida a que al mismo tiempo que se cumplen con varias de las guías citadas se obtiene cierto grado de inmunidad. Veamos.

### II. Promoción de Revisión de Actividades Profesionales

El primer objetivo del estatuto federal es el de promover las actividades de revisión de pares (peer review

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activities) mediante el establecimiento de unos mecanismos que de ser seguidos por la institución se podría acoger a cierta inmunidad de algunas demandas basadas en causas de acciones federales o estatales excepto aquellos que sean bajo leyes federales o estatales de derechos civiles o en ciertas acciones llevadas por el gobierno federal o el Secretario de Justicia estatal y no una persona privada.<sup>6</sup>

En Puerto Rico contamos con legislación que protege a los miembros de comité de garantía de calidad de las facilidades de servicios de salud, a los proveedores de servicios de salud y testigos por actos en el desempeño de las funciones de tales comités, no obstante e independientemente de la ley federal. Veamos, como lee la ley estatal:

Los miembros de un Comité de Garantía de Calidad, los proveedores de servicios de salud y cualquier ciudadano no serán responsables económicamente en acciones de daños y perjuicios por cualquier acto, procedimiento o testimonio realizado o prestado como parte de las funciones del Comité de Garantía de Calidad, siempre y cuando no actúen intencionalmente y a sabiendas del daño que razonablemente se puede ocasionar.

Las impresiones mentales, conclusiones, opiniones o teorías de los miembros de los Comités de Garantía de Calidad que surjan como parte de las funciones de este Comité estarán fuera del alcance del descubrimiento de prueba.<sup>7</sup>

Claramente, dicho precepto legal habla de Comités de Garantía de Calidad. Es nuestra opinión que cuando dice la ley Comité de Garantía de Calidad debe interpretarse como aplicable a todo comité de revisión de pares, en sentido amplio, incluyendo Juntas de Directores de hospitales, Comités de Credenciales, etcétera. Varios comités, con otro nombre, sirven el mismo propósito de velar por la calidad. Entendemos que ésta sería la interpretación correcta pero aconsejamos que se legisle para aclarar este punto pues podrían haber opiniones distintas sobre este punto.

Aparte de esta ley estatal, la ley federal de forma independiente provee cierta inmunidad a las acciones de comités de revisión profesional si se cumplen con varios requisitos, a saber:

#### Section 11112. Standards for professional review actions

##### (a) In general

For purposes of the protection set forth in section 11111

(a) of this title, a professional review action must be taken—

(1) in the reasonable belief that the action was in the furtherance of quality health care.

(2) after a reasonable effort to obtain the facts of the matter.

(3) after adequate notice and hearing procedures are afforded to the physicians involved or after such other procedures as are fair to the physician under the circumstances, and

(4) in the reasonable belief that the action was warranted by the facts known after such reasonable effort to obtain facts and after meeting the requirement of paragraph (3).

A professional review action shall be presumed to have met the preceding standards necessary for the protection set out in section 11111 (a) of this title unless the presumption is rebutted by a preponderance of the evidence.<sup>8</sup>

Lo que constituye aviso y vista adecuada se cumple bajo la ley si se siguen los siguientes requisitos:

##### (b) Adequate notice and hearing

A health care entity is deemed to have met the adequate notice and hearing requirement of subsection (a) (3) of this section with respect to a physician if the following conditions are met (or are waived voluntarily by the physician):

##### (1) Notice of proposed action

The physician has been given notice stating—

(A) (i) that a professional review action has been proposed to be taken against the physicians

(ii) reasons for the proposed action

(B) (i) that the physician has the right to request a hearing on the proposed action.

(ii) any time limit (of not less than 30 days) within to request such a hearing, and

(C) a summary of the rights in the hearing under paragraph (3).

##### (2) Notice of hearing

If a hearing is requested on a timely basis under paragraph (1) (B), the physician involved must be given notice stating—

(A) the place, time, and date, of the hearing which date shall not be less than 30 days after the date of the notice, and

(B) a list of the witnesses (if any) expected to testify at the hearing on behalf of the professional review body.

##### (3) Conduct of hearing and notice

If a hearing is requested on a timely basis under paragraph (1)(B)—

(A) subject to subparagraph (B), the hearing shall be held (as determined by the health care entity)—

(i) before an arbitrator mutually acceptable to the physician and the health care entity.

(ii) before a hearing officer who is appointed by the entity and who is not in direct economic competition with the physician involved, or

(iii) before a panel of individuals who are appointed by the entity and are not in direct economic competition with the physician involved;

(B) the right to the hearing may be forfeited if the physician fails, without good cause, to appear;

(C) in the hearing the physician involved has the right—

(i) to representation by an attorney or other person of the physician's choice.

(ii) to have a record made of the proceedings, copies of which may be obtained by the physician upon payment of any reasonable charges associated with the preparation thereof.

(iii) to call, examine, and cross-examine witnesses.

(iv) to present evidence determined to be relevant by the hearing officer, regardless of its admissibility in a court of law, and

(v) to submit a written statement at the close of the hearing; and

(D) upon completion of the hearing, the physician involved has the right—

(i) to receive the written recommendation of the arbitrator, officer, or panel, including a statement of the basis for the recommendations, and

(ii) to receive a written decision of the health care entity, including a statement of the basis for the decision.

A professional review body's failure to meet the conditions described in this subsection shall not, in itself, constitute failure to meet the standards of subsection (a)(3) of this section.<sup>9</sup>

Como indica el último párrafo citado, se podría cumplir con los requisitos de vista y aviso adecuado en ciertas circunstancias a pesar de no llevar a cabo todos los anteriores mencionados pasos. La ley provee el siguiente mecanismo para casos de emergencia, veamos:



(c) Adequate procedures in investigation or health emergencies

For purposes of section 11111(a) of this title, nothing in this section shall be construed as—

(1) requiring the procedures referred to in subsection (a)(3) of this section—

(A) where there is no adverse professional review action taken, or

(B) in the case of a suspension or restriction of clinical privileges, for a period of not longer than 14 days, during which an investigation is being conducted to determine the need for a professional review action; or

(2) precluding an immediate suspension or restriction of clinical privileges, subject to subsequent notice and hearing, or other adequate procedures, where the failure to taken such an action may result in an imminent danger to the health of any individual.<sup>10</sup>

De cumplirse con los anteriores requisitos habrá básicamente el siguiente tipo de inmunidad:

#### Section 11111. Professional review

(a) In general

(1) Limitation in damages for professional review actions  
If a professional review action (as defined in section 11151(9) of this title) of a professional review body meets all the standards specified in section 11112 (a) of this title, except as provided in subsection (b) of this section—

(A) the professional review body,

(B) any person acting as a member or staff to the body

(C) any person under a contract or other formal agreement with the body, and

(D) any person who participates with or assists the body with respect to the action, shall not be liable in damages under any law of the United States or of any State (or political subdivision thereof) with respect to the action. The preceding sentence shall not apply to damages under any law of the United States or any State relating to the civil rights of any person or persons, including the Civil Rights Act of 1964, 42 U.S.C. 2000e et seq. and the Civil Rights Acts, 42 U.S.C. 1981 et seq. Nothing in this paragraph shall prevent the United States or any Attorney General of a State from bringing an action, including an action under section 4C of the Clayton Act, 15 U.S.C., Section 15C [15 U.S.C.A. Section 15c], where such an action is otherwise authorized.<sup>11</sup>

En resumen hay dos formas de obtener inmunidad, una bajo la ley local, y otra cumpliendo con los requisitos de la ley federal. El tipo de inmunidad varía en cada una de las leyes. Las instituciones hospitalarias deben asesorarse ya que para obtener los beneficios de la inmunidad federal se requiere el cumplir con los requisitos de dicha ley.

### III. Obligación de Reportar Información bajo el Health Care Quality Improvement Act del 1986

Los hospitales vienen obligados a reportar información según provisto por la ley y el reglamento sobre:

1. pagos por impericia médica para el beneficio (de reclamación judicial o extrajudicial) de dentistas, médicos u otros "health care practitioners" dentro de treinta días luego del pago.

2. cualquier acción que el Hospital tome contra un médico (o dentista) que afecte adversamente los privilegios del médico (o dentista) por un período mayor de treinta días basada en la competencia o

conducta profesional del facultativo, y bajo ciertas circunstancias cuando se le acepta la renuncia de privilegios a un médico (o dentista) estando bajo investigación o a cambio de que no investiguen. Esto hay que reportarlo dentro de quince días de lo ocurrido.

Los hospitales tienen el deber de solicitar información al banco de datos cada vez que un médico, dentista o "healthcare professional" solicita privilegios médicos (o de cortesía) o membresía en la facultad y cada dos años en cuanto a todos los médicos, dentistas o "healthcare professionals" que sean miembros de la facultad o que tengan privilegios clínicos en el hospital.

Como la obligación de reportar los pagos hechos por los hospitales en casos de impericia médica para beneficio de dentistas, médicos u otros "healthcare professionals" (aunque sean extrajudicialmente) y la obligación de reportar acciones adversas contra dentistas y/o médicos recae en las instituciones, los hospitales deben enviar dichos informes. Sin embargo, antes de que se envíen dichos informes se debe consultar con asesores de tal manera que no se hagan informes indebidos que puedan afectar a los médicos u otros profesionales de la salud. En caso de pagos por impericia médica los reportes se hacen al Banco de Data y a la Junta Examinadora apropiada. En caso de acciones adversas el reporte se hace a la Junta Examinadora de Médicos o Dentistas según sea el caso.

Finalmente, como indicaremos anteriormente, los hospitales también tiene el deber de *obtener* información del banco nacional de datos. Veamos.

#### Section 11135. Duty of hospitals to obtain information

(a) In general

It is the duty of each hospital to request from the Secretary (or the agency designated under section 11134 (b) of this title), on and after the date information is first required to be reported under section 11134 (a) of this title—

(1) at the time a physician or licensed health care practitioner applies to be on the medical staff (courtesy or otherwise) of, or for clinical privileges at, the hospital; information reported under this subchapter concerning the physician or practitioner, and

(2) once every 2 years information reported under this subchapter concerning any physician or such practitioner who is on the medical staff (courtesy or otherwise) or, has been granted clinical privileges at the hospital.

A hospital may request such information at other times.<sup>15</sup>

En esta sección anteriormente citada es de suma importancia el que se le dé estricto cumplimiento, ya que según la ley se presume que la institución sabe sobre la información reportada. Esto muy bien podría ser utilizado por demandantes como parte de la prueba de que la institución no hizo una buena investigación sobre las credenciales del galeno.

Los anteriores citados artículos son solamente algunos de los artículos aplicables a los hospitales quienes además tienen que velar por el cumplimiento de la ley y su reglamento. Las actividades del Banco de Data serán expandidas por lo que las instituciones deben siempre obtener asesoramiento pertinente.<sup>13</sup>

#### IV. Conclusión y Recomendaciones

En conclusión, recomendamos a las instituciones hospitalarias en particular el fiel cumplimiento de la ley federal lo que redunda en beneficios para la propia institución. El cumplimiento de las secciones de reportar y obtener información según la ley y el reglamento requiere que la institución elabore un sistema y protocolo adecuado que llene los requisitos de dicha ley. Lo discutido en este artículo es una introducción general al tema por lo que cada institución o persona debe obtener el asesoramiento pertinente para cumplir con esta ley y su reglamento. El derecho local sobre notificaciones y reportes no se ha discutido en este artículo pero las instituciones deben asesorarse también sobre el particular.

**Summary:** The most important aspects of the federal law entitled "Health Care Quality Improvement Act of 1986" are discussed in general terms by the author from the point of view of hospital entities in Puerto Rico. In addition, aspects of suspension of privileges, obtention of immunity protection and the obligation to solicit and report information to the National Data Bank under the federal law are also discussed.

#### Notas al Calce

1. Este artículo está basado en un trabajo que preparara el autor durante sus estudios en el curso Aspectos Legales en la Administración de Servicios de Salud, Programa de Maestría en Administración de Servicios de Salud, Escuela Graduada de Salud Pública, Recinto de Ciencias Médicas, Universidad de Puerto Rico.

- Sobre este tema, véase, e.g., Pugsley, *Implementing the Health Care Quality Improvement Act*, Health and Hosp. L., Vol. 23, Nov. 1, p. 42 (1990); Comment, *Physician Heal Thyself: Because the Cure, the Health Care Quality Improvement Act, May be Worse than the Disease*, 37 Cath. U. L. Rev. 1073 (1988); Note, *The Health Care Quality Improvement Act of 1986: Will Physicians Find Peer Review More Inviting?* 74 Va. L. Rev. 1115 (1988); Note, *Physician Staff Privilege Cases: Antitrust Liability and the Health Care Quality Improvement Act*, 29 Wm. & Mary L. Rev., 609 (1988); Colantonio, *The Health Care Quality Improvement Act of 1986: How should Hospitals Respond?* 9 Whittier L. Rev. 277 (1987); Lynch, *The Army's Implementation of the Health Care Improvement Act of 1986*, The Army Lawyer, October 1988; *Immunity for Peer Review Participants in Hospitals: What Is It? Where Does It Come From? How Do You Protect It?*, prepared by the Peer Review Immunity Task Group of the American Academy of Hospital Attorneys of the American Hospital Association (December 29, 1989).
2. Pub. L. Núm. 99-660, 100 Stat. 3784, 42 U.S.C. Sección 11101-11152, según enmendada, Pub. L. Núm. 100-177, 101 Stat. 986, y por Pub. L. Núm. 101-239, 165 Cong. Rec. H. 9365.
  3. 42 U.S.C. Sección 11101.
  4. 106 D.P.R. 72 (1977).
  5. Cruz, Milton. *Suspensión de Privilegios Médicos en la Facultad Médica de un Hospital Privado o de la Comunidad*, Vol. 80 Núm. 10, Bol Asoc Med PR (1988), página 391 ( citas omitidas).
  6. 42 U.S.C. Sección 11111.
  7. 20 L.P.R.A. Sección 52a.
  8. 42 U.S.C. Sección 11112(a).
  9. 42 U.S.C. Sección 11112(b).
  10. 42 U.S.C. Sección 11112(c).
  11. 42 U.S.C. Sección 11111(a).
  12. 42 U.S.C. Sección 11135(a).
  13. Ley Pública 100-93, sección 5, Medicare and Medicaid Patient and Program Protection Act of 1987.



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# Seguimiento a la Ley Federal sobre los Desperdicios Médicos o Biomédicos

Ing. José L. Fortuño

En noviembre 1ro. de 1988, el "Medical Waste Tracking Act" de 1988 (Ley Federal de Seguimiento a los Desperdicios Médicos o Biomédicos) fue firmado como Ley. Esta Ley requiere a la Agencia de Protección Ambiental de los Estados Unidos (EPA) establecer un programa experimental por un término de dos (2) años para el rastreo de desperdicios médicos en estados sujetos al programa, aunque los desperdicios sean sacados finalmente fuera del estado para su tratamiento o disposición. La reglamentación que establece este programa exige un listado de los desperdicios médicos a rastrearse y unos parámetros mínimos de segregación de éstos, su empaque o identificación antes de ser transportados para el tratamiento y/o a las facilidades de disposición. Las organizaciones o instituciones que determinen procesar mediante la incineración sus desperdicios, también deben responder a requerimientos específicos insalvables.\*

La Agencia Federal de Protección Ambiental levantará datos de los estados participantes a los fines de rendirle al Congreso varios informes acerca del éxito de la ley y recomendaciones sobre cómo legislar acerca de los desperdicios biomédicos y patológicos.

El Estado Libre Asociado de Puerto Rico, a través de la Junta de Calidad Ambiental, fue incluido en dicho programa y el 24 de junio de 1989 inició formalmente sus actividades para ponerlo en vigor. La Sección 11007 de la Ley Federal provee un mecanismo legal mediante el cual los estados (y Puerto Rico) podrían llevar a cabo una auditoría para velar porque se cumplan los requisitos de la ley y los reglamentos federales de la Agencia Federal de Protección Ambiental.\*

¿A quién es aplicable? Según el artículo publicado por el Sr. Rafael Faria, el rastreo de los desperdicios médicos, la ley y el reglamento es aplicable a las oficinas profesionales, instituciones, y comercios, tanto gubernamentales como privadas, que generen desperdicios médicos. Entre ellos podemos mencionar hospitales, oficinas profesionales de médicos, dentistas, veterinarios, funerarias, laboratorios de investigación, laboratorios clínicos, y otros.

\*Rohena Betancourt, Santos

- Los desperdicios médicos y patológicos en Puerto Rico.
- Los Requerimientos del "Medical Waste Tracking Act" y su Implementación por la Junta de Calidad Ambiental.

\*(40 CFP 22 and 259, Standards for Tracking and Management of Medical Waste; Interim Final Rule and Request for Comments, Page 12326).

- Ponencia presentada en el Hotel Condado Beach, auspiciada por el Instituto de Aprendizaje e Investigación Jurídica.

Los desperdicios médicos se categorizan de las siguientes formas:

- Cultivos y cultivos (madres) de agentes infecciosos.
- Desechos patológicos humanos, incluyendo los que son obtenidos de procedimientos quirúrgicos y autopsias.
- Sangre humana y productos de sangre.
- Objetivos cortantes y punzantes usados.
- Desechos de animales que se han contaminado durante programas de investigación médica.
- Desechos generados por pacientes que están en zonas de aislamiento por sufrir enfermedades contagiosas.
- Algunos objetos cortantes y punzantes que se desechan sin usarse.
- Desechos de procesos de diálisis.

¿Qué podemos hacer para manejar efectivamente los desperdicios médicos y cumplir con los requerimientos de tratamiento?

La ley requiere que los métodos que se utilicen para el tratamiento de los desperdicios transformen los mismos de tal forma que sean irreconocibles. Para lograr esto es necesario utilizar el triturador de desperdicios, con excepción del método de incineración.

Los métodos de tratamiento disponibles hasta el momento son:

## Incineración

Ventajas	Desventajas
* Se puede disponer de la mayoría de los desperdicios	* Al costo de capital
* Deseable para volúmenes altos de desperdicios	* Altos costos de mantenimiento
* Marcada reducción de volumen y peso	* Emisión a la atmósfera y sus implicaciones
* Esteriliza y detoxifica	* Difícil de localizar una unidad de incineración
* Recuperación de calor	* Dificultad en la adquisición de permisos
* Residuos irreconocibles	* Oposición pública

## Esterilización por Vapor

Ventajas	Desventajas
* Bajo costo	* Capacidad limitada
* Poco espacio requerido	* no se ajusta a todos los desperdicios

- \* Simplicidad del proceso
- \* Se manejan grandes cantidades de bolsas
- \* Control de olores
- \* Volumen de tratamiento fijo
- \* Apariencia no cambia

### Desinfección Química y Trituración

#### Ventajas

- \* Reducción sustancial del volumen
- \* Deseable para la mayoría de los desperdicios
- \* Relativamente simple
- \* Altera la forma y apariencia de los desperdicios

#### Desventajas

- \* Costo relativamente alto
- \* Manejo de los desperdicios
- \* Capacidad limitada
- \* Efluente contaminante
- \* Niveles altos de ruido y químico
- \* Experiencia mínima

Inactivación termal e irradiación, oxidación mojada, y otras son nuevas tecnologías que están surgiendo, de las cuales se conoce muy poco todavía.

Los requisitos de segregación, empaque, rotulación, almacenaje, y registros de información de tratamiento, cantidad generada, y otros están detallados claramente en la ley, por la que no entraremos en ellos.

Debemos señalar que cuando hablamos de segregación nos referimos a la separación de los desperdicios, de acuerdo a su categoría:

o punantes, tales como: agujas, cristales, bisturí.

- \* Fluidos en cantidades mayores de 20cc.
- \* Otros desperdicios médicos regulados como: partes humanas, gasas impregnadas de sangre, y animales utilizados en procesos de investigación.

¿Qué alternativas tenemos para el manejo y disposición final de estos desperdicios?

Entre las alternativas a considerarse podemos mencionar las siguientes:

- Segregación en la fuente, empaque, tratamiento, y disposición final por el generador.
- Segregación y empaque por el generador; transportación, tratamiento, y disposición final por un contratista independiente cualificado. (En la actualidad existen en Puerto Rico siete (7) contratistas independientes.)
- Los generadores pequeños, como por ejemplo las oficinas médicas, podrían utilizar un mismo contratista independiente para la transportación, tratamiento y disposición final. Usualmente el contratista independiente posee su propio recipiente de empaque, el cual puede almacenar cerca de 50 a 60 libras, lo que hace viable que los generadores pequeños compartan los gastos de disposición final. (Los costos de transportación, tratamiento, y disposición final fluctúan entre 40 y 55 centavos por libra o 25 dólares por caja.

El establecimiento de un Comité Timón como organismo rector de la política sobre el manejo de desperdicios médicos, fue el comienzo del involucramiento y concientización a todos los niveles de la problemática del manejo de los desperdicios.

Para la implantación del Programa de Manejo de Des-

perdicios Biomédicos, en el Hospital San Pablo se comenzó con la selección de un técnico de desperdicios biomédicos, el cual se orientó y adiestró en todo lo relacionado a la ley y los reglamentos. Luego se procedió a seleccionar los materiales y equipo necesarios para la segregación en la fuente, recogido, empaque, almacenamiento, y la compañía que se encargaría de la disposición final.

Un plan de adiestramiento dirigido a todo el personal de la Institución fue el comienzo para una segregación efectiva de los desperdicios; esta fase fue clave en el éxito del plan piloto que se estableció en las áreas de Sala de Operaciones e Intensivo.

El programa se ha establecido en su totalidad, y en la actualidad tres (3) técnicos de desperdicios biomédicos manejan alrededor de 2,500 libras de desperdicios diariamente.

El readiestramiento al personal es continuo y se estableció como parte del programa de adiestramiento al personal nuevo una sección dirigida al manejo efectivo de los desperdicios biomédicos.

Recientemente hemos establecido un programa de orientación a la Facultad Médica, en el cual mediante el asesoramiento técnico le ayudamos a implantar su propio programa de desperdicios biomédicos en sus oficinas privadas.

La orientación consiste básicamente en lo siguiente:

- Requerimientos de la ley y reglamentos
- Aplicación específica a su práctica
- Alternativas de equipo y materiales
- Adiestramientos disponibles para el personal
- Documentación requerida
- Alternativas para el manejo efectivo de los desperdicios
- Evaluación del proceso en términos de efectividad en el cumplimiento de la ley

La ley y los reglamentos están en vigor y las alternativas para el cumplimiento de la ley existen, por lo que todo generador responsable debe proceder con la alternativa que más se ajuste a sus necesidades específicas. El ambiente y la salud es responsabilidad de todos. ¡Conservémoslo!

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Ponencia presentada en el Hotel Condado Beach, auspiciada por el Instituto de Aprendizaje e Investigación Jurídica.



# SOCIOS NUEVOS



## ACTIVOS

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**García Rivera, Roberto A MD** - Escuela de Medicina San Juan Bautista, Bayamón, Puerto Rico, 1981. Fisiatría. Ejerce en Mayagüez.

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**González Olivieri, Radamés MD** - Escuela de Medicina de la Universidad de Valencia, España, 1982. Cirugía. Ejerce en Ponce.

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## INTERNOS-RESIDENTES

**Mendoza Villahermosa, Odalys MD** - Escuela de Medicina de la Universidad de Puerto Rico, 1989. Oftalmología. Ejerce en Bayamón.

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## REINGRESOS-ACTIVOS

**Izaguirre Vidal, Bernardo MD** - Escuela de Medicina de la Universidad de Valladolid, España, 1975. Pediatría. Ejerce en Santurce.

**Jiménez Méndez, Rafael A MD** - Escuela de Medicina de la Universidad Santiago de Compostela, España, 1974. Pediatría. Ejerce en Camuy.



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## AMERICAN ACADEMY OF PEDIATRICS

### AAP UPDATES HIB VACCINE RECOMMENDATION

In an updated policy statement, the American Academy of Pediatrics (AAP) now recommends a Hib vaccine (*Haemophilus influenzae* type b conjugate vaccine) for all children at 15 months of age. Previously, the AAP recommended the vaccine at 18 months of age.

The AAP's Committee on Infectious Diseases revised its position after reviewing data on 15 month old children immunized with the three conjugate vaccines licensed by the U.S. Food and Drug Administration (FDA).

The statement, published in the July issue of *AAP News*, noted that *Haemophilus influenzae* type b is a major cause of meningitis, pneumonia and other serious infections in infants and children, and these recommendations aim to decrease the large number of Hib cases in the United States.

"Prior to the introduction of immunization against *H. influenzae* type b, it was estimated that annually approximately 16,000 cases of invasive infection occurred in the United States in children 5 years of age or younger," the AAP statement said. "About 26.6 percent of cases occurred in children 18 months of age or older, and approximately an additional 9.3 percent occurred in children 15 to 17 months of age. Thus, about 35.9 percent of the disease burden is potentially preventable by an effective vaccine administered at 15 months of age."

The AAP further recommends:

- \* For children 18 months of age or older who have not yet been immunized against *H. influenzae* type b disease, immunization continues to be recommended up to the fifth birthday after which the risk of disease is small in healthy children.
- \* Children immunized at 15 months of age or older need not be reimmunized.
- \* Any of the Hib conjugate vaccines may be simultaneously administered with polio vaccine, measles-mumps-rubella (MMR) vaccines, or diphtheria-tetanus-pertussis (DTP) vaccines.

- \* Children who experienced *H. influenzae* type b disease before 24 months of age should receive a dose of a Hib conjugate vaccine because the disease may not have rendered them immune. Unimmunized children whose disease occurred at 24 months of age or later do not need immunization because the disease most likely rendered them immune.
- \* *H. influenzae* type b conjugate vaccines are not recommended for infants younger than 15 months of age.

### STUDY: POOR IMITATION, PLAY SKILLS CLUES TO AUTISM IN YOUNG CHILDREN

A new study suggests that measuring play and imitation skills may help diagnose autism in young children.

Published in the August issue of *Pediatrics*, the journal of the American Academy of Pediatrics (AAP), the study reveals that young autistic children have weak motor imitation and immature play skills and that these characteristics are relatively specific to this disorder.

The study examines play and imitation skills of 91 children (57 males, 34 females) between three and six years of age to determine their effectiveness in distinguishing autism from mental retardation and other communication disorders. Twenty two autistic children were compared with 15 mentally retarded, 15 hearing-impaired, 19 language-impaired and 20 non-handicapped children.

The authors, from the Vanderbilt University School of Medicine, Nashville, Tennessee, and the University of Miami School of Medicine, Miami, Florida, cite that imitation skills were the most important characteristic differentiating the autistic children from non-autistic handicapped children and may prove to be the most fruitful for screening.

According to the authors, although autism is chronic, early intervention programs may improve behavior. "Weak skills in these areas, in the presence of other autistic symptoms such as poor social and communication skills, may serve as 'red flags' in young children, alerting pediatricians to the possibility of autism," they said.

In the study, each child was observed through a one-way mirror and videotaped in a free-play situation and then in imitation play in a one-on-one situation.

In free play, the children's behaviors were scored by number of toys used, time spent playing with toys, time spent playing with toys appropriately and level of toy play. The toys included wooden blocks, toy cars, a kaleidoscope, dolls and doll furniture, animal puppets, a toy phonograph, a tea set and a toy telephone.

In imitation play, 12 motor tasks were presented and the child's responses were recorded. Eight involved actions with objects, such as stirring a spoon in a cup, petting a stuffed animal, and four involved body move-

ments alone, such as clapping hands, wiggling a thumb.

The autistic children spent less time interacting with and using toys in a functional, conventional manner and engaged in fewer play acts compared with all other groups of children. In comparison, their imitation skills were also significantly weaker.

The study notes that imitation skills emerged as the most important differentiating measure between the autistic group and the other groups of children with overlapping symptoms.

Autism is a developmental disorder characterized by impaired social interactions, a broad range of communication problems ranging from mutism to unusual speech and a restricted range of activities and interests.

### **AAP RECOMMENDS CHILDREN AND ADOLESCENTS AVOID WEIGHT LIFTING UNTIL PHYSICALLY MATURE**

The American Academy of Pediatrics (AAP) says that well-supervised strength training programs for young athletes can increase strength without significant injury. But the Academy cautions that children and adolescents should avoid weight lifting, power lifting and body building until they are physically mature.

The Academy's Committee on Sports Medicine and Fitness says physical maturity is about 15 years old in both sexes, although this will vary with individual development.

The Academy notes that strength training programs for children and adolescent athletes should be permitted only if conducted by well-trained adults. Strength training uses a variety of methods, including exercises with free weight and weight machines, to increase muscular strength, endurance, and/or power for sports participation or fitness enhancement.

In a statement released today in September's *AAP News*, the Academy says that some children and many adolescents use weights to increase strength or enlarge muscle, and a smaller number compete in weight lifting, power lifting, and body building events.

"Over 600 teenagers are registered with the U.S. Weight Lifting Federation, and more than 3,000 with the U.S. Power Lifting Federation," the AAP states. Limited available data indicate that these sports have a significant injury risk.

The AAP notes that because there is very little existing data available on the rate of injury at different ages, it is difficult to determine when young athletes should be allowed to lift maximal amounts of weight. (This is the amount of weight that can be lifted one time and one time only). The U.S. Weight and Power Lifting Federations recommend age 14. Other experts suggest age 16.

"Given the widely varying tempo of pubertal development among adolescents, a more appropriate guideline is one based on physical maturation," the AAP states.

Research has shown that short-term strength training programs can increase strength without significant injury if younger athletes are trained and supervised by

knowledgeable adults. However, the AAP cautions that these studies did not evaluate the relationship between improved strength, injury prevention, or enhanced athletic performance, and no data exist defining injury risks in less organized programs.

The strength training program must be carefully planned in order for it to be safe. A program should be devised for the intensity, duration, frequency, and rate of progression of weight use, as well as selection of sport-specific exercises appropriate for the physical maturity of the individual, the AAP says.

## **Cardiology News**

### **THREE ASSAYS PROMISE RAPID, SENSITIVE AND SPECIFIC DIAGNOSIS OF MYOCARDIAL INFARCTION**

Investigators reported on the development of three new assays that provide rapid, sensitive and specific diagnosis of myocardial infarction (MI).

A Baylor College of Medicine, Houston, Tex. team had developed a rapid (20-minute) and convenient assay for creatine kinase (CK) MB subforms that is a reliable method for diagnosing MI in the initial hours after onset.

The assay was compared to a conventional CKMB assay in 427 serial samples obtained from 172 patients who had been admitted to the hospital with chest pain. Of the group, 55 patients were diagnosed as having MI by conventional means.

Normal plasma contains between 45% 63% of CKMB (mean + 1SD) as the MB2 (tissue) subform. Values above 70% are considered positive for MI. The team led by Peter Puleo, M.D. found in comparing the two assays that the predictive value of a negative subform assay was 96% by four hour after the onset of chest pain. The conventional CKMB assay did not reach this degree of accuracy until nine hours after the onset of chest pain. The MB subform assay's five-hour lead in accurately excluding MI takes on particular significance in regard to thrombolytic therapy, the Baylor team stressed, since thrombolysis must be started immediately for maximum myocardial salvage. The MB subform assay will allow patients without MI to be detected quickly so that therapy can be discontinued or withheld. For example, using the criteria MB2 >70% the proportion of patients correctly diagnosed with acute MI was 20% when seen within two hours, 54% at two to four hours, 87% at four to six hours, and 100% thereafter. These place the assay two to four hours ahead of the conventional MB.

### **CLC1 Radioimmunoassay**

Philip Nicol, M.D. and his team from Massachusetts General Hospital in Boston, developed a very sensitive monoclonal peptide-based cardiac myosin light chain one (CLC1) radioimmunoassay that has absolute cardiac



specificity and makes it possible to detect myocyte necrosis.

The test described by the Boston team is extremely sensitive, and can detect as little as 100 pg(0.0037um) of CLC1 in human serum. Assays of sera from 10 healthy volunteers showed that normal serum does not contain CLC1. Further study showed that the two-hour nonequilibrium test was as sensitive for CLC1 as an overnight equilibrium assay.

#### Cardiospecific Enzyme Immunoassay

North of the border in Toronto, Canada, George Jackowski, M.D. and his colleagues at Toronto General Hospital and Vioclone Biologicals have developed a cardiospecific enzyme immunoassay that quantitates the amount of human ventricular myosin light chain one (HVLC1) "within minutes". The assay provides rapid and early diagnosis of MI and unstable angina.

In 68 patients, including 50 with MI and 18 with unstable angina, the Canadian team quantitated HVLC1. Levels were elevated in 57% of the MI patients one hour after the onset of chest pain, in 65% at four hours and in 76% at eight hours after the onset of chest pain. Other laboratory markers of MI, including CK and CKMB, were slower in providing a diagnosis. CK and CKMB levels were elevated in 0% of patients at one hour, in 5.3% of patients at four hours and in 75% of patients at eight hours after the onset of chest pain.

The HVLC1 assay also assists in the confirmation of unstable angina. In patients with unstable angina, 83% of those with persistently high levels, averaging 6.2 ng/mL compared to a normal level of less than 0.75 ng/mL, had complications or required emergency intervention compared to 16.7% of the patients with low (an average of 2.4 ng/mL) or falling HVLC1 levels.

The rapid new assay not only assists in confirming MI and unstable angina, the researchers noted, it may have prognostic value in managing patients with unstable angina.

#### LONG-TERM LEFT VENTRICULAR FUNCTIONAL IMPROVEMENT PREDICTED

A Duke University Medical Center team in Raleigh, NC, reported that the improvement in regional and global wall motion that occurs seven days after thrombolytic therapy is a good indication of eventual left ventricular improvement. They based this conclusion on an evaluation of serial changes in regional and global left ventricular function measured by contrast angiography in 100 patients after thrombolytic therapy. Studies were performed on these patients immediately after thrombolytic therapy and at seven days and six months later. A comparison of the changes that had occurred at seven days with those that were apparent at six months showed no differences; this was true in patients with occluded infarct-related arteries and patients with patent vessels. Yet, the benefit of thrombolysis has been well established.

Kevin Harrison, M.D. and his colleagues concluded that seven days is an adequate end point for clinical

evaluation of patients who undergo thrombolytic therapy since wall motion changes are evident at the time, and there are no differences in later studies. This absence of change in serial global function, they added suggests that "the clinical benefit of thrombolytic therapy may be unrelated to left ventricular function."

#### NO STROKE RISK LINKED TO ATRIAL ENLARGEMENT IN PATIENTS WITH ATRIAL FIBRILLATION

A Danish team determined that enlargement of the left atrium in patients with chronic atrial fibrillation is not linked to a risk for thromboembolic events. They based their conclusion on a comparison made retrospectively between 25 patients who had chronic atrial fibrillation and suffered strokes and a closely matched control group who also had chronic atrial fibrillation but who did not have any thromboembolic events. Both groups had enlargement of the left atrium as a result of chronic atrial fibrillation.

The two patients groups were part of a larger study being conducted by the investigators, who are from the Rigshospitalet in Copenhagen, Denmark, that includes 336 patients with chronic atrial fibrillation and other serious arrhythmias. The control group comprised patients who had sustained strokes, matching them in age, gender, underlying etiology and duration of atrial fibrillation, history of myocardial infarction, chest pain and heart failure. Left atrial size had been measured by echocardiography in an earlier stage of the study, before patients had suffered strokes.

Follow up for the entire group was at 15.5 months. At this time, mean left atrial dimensions were 49 mm<sup>2</sup> and 50 mm<sup>2</sup>, respectively. Even after corrections were made for body surface area, there was still no difference between the two groups. The Danish team led by Palle Petersen, M.D., concluded that left atrial size is not useful in predicting which patients with chronic atrial fibrillation are at risk for thromboembolic complications.

#### CHANCES OF SURVIVAL CAN IMPROVE WITH LATE REPERFUSION

West German investigators examined the potential benefit of late reperfusion of the artery occluded by infarction on left ventricular function and came up with good news: even late reperfusion can improve the patient's chances of survival.

#### ISAM Trial

Their conclusions were based on data from 368 patients. All the patients, who are part of the I.V. Streptokinase and Myocardial Infarction (ISAM) trial which the West German team from the Klinikum Steigltz in Berlin is conducting, had received either strep-

tokinase or a placebo. But their records showed that early reperfusion did not occur because these patients reached peak creatine kinase MB levels more than 15 hours after the onset of symptoms.

Examination of angiographic studies performed one month after myocardial infarction (MI) showed that late reperfusion occurred in 74 of 116 patients who received streptokinase (64%) and in 141 of 252 patients (56%) who received a placebo. The group with late reperfusion had a mean left ventricular ejection fraction of 56% as compared to 50% in the group without late reperfusion. In the group that received streptokinase, ejection fractions averaged 59% in those with late reperfusion vs. 53% in the others. Patients treated with a placebo had

and average 55% ejection fraction in those with late reperfusion vs. 47% in the others. By 31 months, 8% of the patients with late reperfusion had died compared to 28% of the patients in whom the infarct-related artery continued to be occluded.

Even if reperfusion is delayed after MI, T. Lindner, M.D. and his colleagues observed, the restoration of patency in the infarct-related artery preserves left ventricular function and improves the patient's chances of survival. This finding, they added, should stimulate interest in initiating thrombolytic therapy in patients who do not come to the physician's attention until relatively "late" after MI, currently the subject of active investigation in the United States.

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Among many young women, smoking is viewed as stylish.

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## PNEUMONIA IMMUNIZATION SAVES LIVES, MONEY

Elderly and high risk patients should be vaccinated against pneumococcal infection to prevent their readmission for pneumonia, according to a study in the *Journal of the American Medical Association*.

"Hospitals that immunize discharged patients would, for the most part, prevent pneumonia readmissions to their own institutions," writes David S. Fedson, MD, of the University of Virginia Health Sciences Center, Charlottesville, Va., and colleagues. Pneumococcal infections account for 30-50 percent of all adult community-acquired pneumonia cases requiring hospital admission.

A retrospective study of 1,633 pneumonia patients from the Shenandoah region of Virginia discharged in 1983 "showed that 61-62 percent had been discharged within the previous four years. Among these patients, 87 percent had had one or more high-risk conditions recognized during previous hospital admissions," the authors write.

Previous conditions included cardiopulmonary, cerebrovascular, and renal diseases and diabetes mellitus. Discharged patients had a 6-9 percent probability of readmission with pneumonia within five years, the study found.

"Each such readmission could be prevented by immunizing few (approximately 100) discharged patients with pneumococcal vaccine," the authors write. "The costs of vaccination would be approximately one-third the costs of hospital care for unvaccinated discharged patients readmitted with pneumonia."

In 1988, Medicare reimbursed each hospital an average of \$2,688 per pneumonia discharge; the cost of each vaccine was \$9.60. "Thus, Medicare reimbursement for one pneumonia discharge in 1988 would have been sufficient to immunize approximately 280 previously discharged patients," they write.

"While the Immunization Practices Advisory Committee and other expert panels uniformly recommend pneumococcal immunization for high-risk populations... only 10 percent of the target population have been

immunized - a painful reminder of the limited impact of public health policy statements on medical practice," write Benjamin Schwartz, MD, and Robert F. Brieman, MD, both of the Centers for Disease Control, in an accompanying editorial.

Schwartz and Breiman write that health maintenance organizations and public clinics have strong incentives to immunize based on costs. "Demonstrating a financial incentive for immunization is less likely to influence policies of hospitals, which benefit by providing care, not by preventing admissions," they write. "For hospitals to establish immunization policies, a combination of humanitarian appeals, financial incentives and regulations may be required. One reasonable incentive would be to increase reimbursement to hospitals for pneumococcal immunization commensurate with the number and cost of admissions prevented."

*JAMA September 5, 1990*

## HEART DISEASE RISK DEVELOPS IN EARLY CHILDHOOD: STUDY

Eating and exercise habits formed in early childhood may influence the risk of adult cardiovascular disease, concludes a study in the *Journal of the American Medical Association*.

Even before they reach age seven, children exhibit some of the same risk factors for heart disease as do adults, say Bernard Gutin, PhD, of the Departments of Movement Sciences and Education, Columbia University, New York, N.Y., and colleagues.

"There is evidence cardiovascular disease originates during childhood," they report.

Their study is the first to examine the separate and combined effects of fitness and fatness, including the relationship of blood pressure to fat distribution, in young inner-city children.

Previous studies have concluded that American children are getting fatter, and pediatric hypertension associated with obesity is on the rise. This "suggests that the next generation may suffer from a good deal of preventable cardiovascular disease," the authors say.

The researchers studied blood pressure, aerobic fitness and fatness in 216 primarily Hispanic inner-city 5- and 6-years-old children of low-income parents. Study subjects (109 boys, 107 girls) were recruited mainly from an outpatient pediatric clinic in upper Manhattan.

Four blood pressure (BP) readings were taken, then averaged, for each child. Two treadmill tests were administered, and the results also were averaged to provide a measurement of the child's aerobic fitness.



Fatness was measured by using Lange calipers at five skin folds along the right side of the child's body. The researchers also collected information on the children's diets.

"Significant relations" were found in aerobic fitness and diastolic BP in both boys and girls. Diastolic BP was inversely related to fitness in both sexes, and positively related to fatness in boys," they write. "Systolic BP was positively related to fatness for the boys and girls."

Young boys were more aerobically fit than young girls. Total body mass did not differ significantly between the sexes. However, significant sex differences were found in the pattern of fat deposition: girls had more fat in the peripheral skin folds (such as in the thighs and triceps) than in the central skin folds (such as in the abdomen). The pattern of fat distribution seen in the children was similar to that found in the adult population, the authors say. Fat patterning was related to BP only in the boys.

The authors found no significant association between dietary factors (such as caloric intake) and the relationships between fitness, fatness, and blood pressure.

"It seems that already at 5 and 6 years of age fitness and fatness have an impact on current and future cardiovascular health," say the authors. This highlights "the potential value of early intervention for prevention of cardiovascular disease," they conclude.

*JAMA September 5, 1990*

#### STUDY: THYROID MARKERS MAY POINT MISCARRIAGE RISK

Pregnant women with thyroid autoantibodies are more likely to suffer early miscarriage than those who do not have the antibodies, concludes a study in the *Journal of the American Medical Association*.

These autoimmune "markers" may be used to test a woman's risk of miscarriage, say the authors, Alex Stagnaro-Green, MD, of the Division of Endocrinology, Mount Sinai School of Medicine, New York, N.Y., and colleagues. Their study is the latest indication that maternal autoimmune conditions play an important role in pregnancy loss.

Using the highly sensitive enzyme-linked immunosorbent assay (ELISA), the researchers screened 552 women during their first trimester of pregnancy for the presence of thyroid autoantibodies. Of these, 108 (19.6 percent) tested positively for thyroid autoantibodies and 444 (80.4 percent) were negative. They then collected information on whether the women miscarried, carried the pregnancy to term and delivered, or had an elective abortion.

Of 492 women available for follow-up, 10.2 percent suffered a miscarriage. Seventeen percent of women who had positive tests miscarried, compared with 8.4 percent of the autoantibody-negative women. Positivity for thyroid autoantibodies was "significantly associated with an increased pregnancy loss," the authors report.

While individual levels of thyroid autoantibodies were related to an increased rate of miscarriage, factors such as maternal age, gestational age, previous childbearing

history, and levels of thyroid hormone did not affect the miscarriage rate.

"The mechanism by which thyroid autoantibodies are related to miscarriage probably reflects generalized activation of the immune system," say the authors. This may be an inherited trait or "a consequence of early immune interactions resulting in rejection of the fetus," they say.

"Because spontaneous miscarriage has recently been shown to occur in up to 31 percent of all pregnancies, it will be important to examine further the prevalence of thyroid autoantibodies in women with spontaneous pregnancy loss," the authors write. Early identification of "at-risk" pregnancies "may eventually provide the opportunity for intervention and prevention," they conclude.

Recurrent miscarriage (usually defined as three consecutive losses) "occurs in 0.5 percent to 1 percent of women, an incidence equal to or exceeding that of most major medical problems," writes D. Ware Branch, MD, of the Department of Obstetrics and Gynecology, University of Utah School of Medicine, Salt Lake City, in his accompanying editorial.

Dr. Stagnaro-Green and coworkers "have opened a new avenue of investigation in the study of pregnancy loss, but the extent of the problem, its contribution to recurrent pregnancy loss, and the important question of cause-and-effect remain unresolved," he writes.

*JAMA September 19, 1990*

#### INCIDENCE OF SYPHILIS RESISTANT GONORRHEA UP

Two studies in the *Journal of the American Medical Association* indicate that gonorrhea and syphilis persist as health problems.

One study found that syphilis in the U.S. is at its highest levels since 1949. Rates of primary and secondary syphilis increased 34 percent from 1981 to 1989, according to the study done by Robert T. Rolfs, MD, and Allyn K. Nakashima, MD, both of the Division of Sexually Transmitted Diseases/Human Immunodeficiency Virus Prevention at the Centers of Disease Control, Atlanta, Ga. Syphilis rates increased from 13.7 to 18.4 cases per 100,000 population.

"Behind this important overall rise, much larger changes in the incidence of syphilis occurred in certain subpopulations," Rolfs and Nakashima write. The data came from quarterly and annual reports of syphilis sent to the CDC by state health departments from 1981 through 1989.

From 1982 to 1985, syphilis decreased from 101.9 to 71.5 cases per 100,000 population among black men, and from 45.8 to per 100,000 among black women. "However, in 1986 this trend reversed, and the incidence among blacks more than doubled from 1985 to 1989 (52.6 to 121.8 cases per 100,000 persons)," the authors found.

"The increase was greater for black women (176 percent increase, from 35.8 to 98.7 cases per 100,000)

than for black men (106 percent increase, from 71.5 to 147.4 cases per 100,000)," they write. For white males, however, syphilis rates dropped from 10.3 cases per 100,000 in 1982 to 3.2 cases per 100,000 in 1989. Incidence remained low and unchanged for white women.

Rates for Hispanic women increased 69 percent to 13.7 cases per 100,000 population by 1988, but then dipped to 10 cases per 100,000 in 1989. The authors also found cases for Hispanic men changed little from 1981 to 1987, after which they decreased 37 percent to 27.3 cases per 100,000 by 1989.

The authors suggest one reason for the rise in syphilis cases among blacks is the interaction of substance abuse and sexual behavior.

"Trends in syphilis incidence indicate changes in sexual behavior that may be important [in determining] future sexual transmission of human immunodeficiency virus," the authors write. "If prevalence of genital ulceration affects the pattern of spread of HIV in Africa as much as in the United States, these data suggest that portions of the U.S. population may be at great risk of experiencing the rapid spread of HIV seen among heterosexuals in Africa."

The second study, that of treatment-resistant strains of *Neisseria gonorrhoeae*, found "although the incidence of gonorrhea decreased since 1975, infections caused by antimicrobial-resistant gonococci have become an increasing problem."

Data from the Gonococcal Isolate Surveillance Project were used to study 6,204 isolates from 21 clinics nationwide. "Twenty-one percent met at least one of the surveillance criteria for resistance to penicillin, tetracycline, cefoxitin, or spectinomycin," writes author Sandra K. Schwarcz, MD, MPH, of the Division of Sexually Transmitted Diseases, Centers for Disease Control, Atlanta, Ga., and colleagues.

"These results demonstrate the wide distribution of antimicrobial-resistant *N. gonorrhoeae* and support recent changes in Centers for Disease Control therapy recommendations for gonococcal infections that no longer recommend tetracycline and penicillin as first-line therapies," the authors write.

The current first-line therapy for gonorrhea is a single injection of ceftriaxone combined with seven days of oral doxycycline. The authors found all isolates were susceptible to ceftriaxone.

In an editorial on the two studies, H. Hunter Handsfield, MD, director of the STD Prevention Program at the Harborview Medical Center, Seattle, Wa., writes that "public health practitioners and practicing physicians are ultimately in the same boat as professionals seeking to prevent STDs and their ravages. We can do that only if we work together, not apart."

Handsfield writes that while substance abuse may have a specific influence, "the underlying problems are unemployment, poverty, poor education, prejudice, and inadequate health care, which in turn lead to crime, prostitution, substance abuse, family disruption, and despair. All these factors combine to create an atmosphere conducive to the spread of STDs, a situation with ample historical precedence."

*JAMA* September 19, 1990

## STUDIES FIND SMOKING AND DEPRESSION HIGHLY CORRELATED

Smokers are more likely than nonsmokers to suffer from major depressive disorders, says a study in the *Journal of the American Medical Association*.

In a related *JAMA* study, depressed smokers were less able to "kick the habit" when compared with nondepressed smokers.

The two studies may lend further support to the "self-medication" theory of substance abuse: people become addicted to certain drugs to combat painful feelings and help the user feel more "normal."

A study by Alexander H. Glassman, MD, of the New York State Psychiatric Institute, New York, and colleagues, is the first to demonstrate a relationship between smoking and major depression using entirely community-based data. They analyzed data collected in St. Louis, Mo., in the early 1980s as part of national survey of the prevalence of psychiatric illnesses. The researchers defined major depression as a depressed mood which persists for two or more weeks coupled with four or more depressive symptoms (e.g., loss of appetite, sleep disturbance).

Five percent of the 3,213 survey respondents had suffered from a major depressive disorder some time in their lives. Among respondents who had never smoked, the prevalence of major depression was 2.9 percent; among those who smoked daily for at least a month, the rate jumped to 6.6 percent.

"This association between smoking and depression exists not just among patients presenting to a psychiatrist for treatment but also among everyone with a lifetime diagnosis of major depression, whether or not they ever sought treatment," write the authors.

The association between depression and smoking was not uniform across other psychiatric conditions studied. Although smoking is often linked to anxiety and tension, there was no significant relationship between smoking and the anxiety-related diagnoses of phobia, panic and obsessive-compulsive disorders after depression was excluded from analysis. However, the researchers did find a high rate of smoking among alcoholics in the sample.

Smokers without a lifetime history of major depression were more than twice as likely as depressed smokers to successfully quit smoking, the authors report. They theorize, however, that "when individuals with a history of major depression stop smoking, depressive symptoms, and, in some cases, serious major depression may ensue."

Depression impedes a smoker's ability to quit, concludes a study by Robert F. Anda, MD, MS, of the Division of Chronic Disease Control and Community Intervention, Centers for Disease Control, Atlanta, Ga., and colleagues. They found depressed smokers were 40 percent less likely to have stopped smoking compared with nondepressed smokers.

The researchers analyzed data from two national health and nutrition studies. Using a standardized depression index, the authors found that smoking rates



increased and success in quitting decreased as the score on the depression scale rose. Twenty percent of those who smoked at least one pack of cigarettes per day had high depressive symptom scores.

The authors estimate that after nine years of follow-up, 17.7 percent of nondepressed smokers had quit, while only 9.9 percent of depressed smokers had successfully stopped smoking.

"Because depression appears to reduce a smoker's ability to quit, it is likely that in the future the prevalence of depression will be even higher among smokers," the authors conclude.

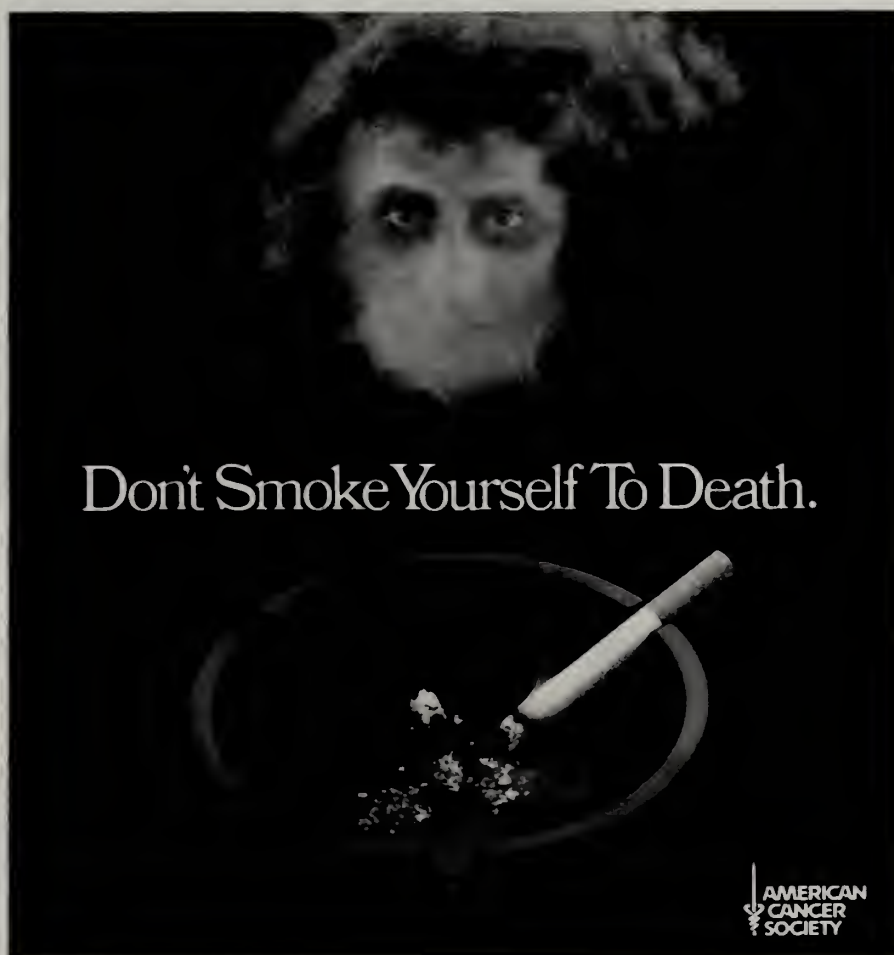
"Further research is needed to understand the mechanisms that explain the relationship between

smoking and depression and to determine whether smoking cessation is facilitated by treatment of depression," they write.

In an accompanying editorial, Richard M. Glass, MD, of the American Medical Association believes it is still too early to "recommend routine use of antidepressant treatment to assist smoking cessation for all smokers with a history of depression."

"Evaluation and treatment of depression may become essential aspects of the role physicians need to play in the campaign to achieve a smoke-free society," he says.

*JAMA September 26, 1990*





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DICIEMBRE 1990

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# Columna del Editor



Con la publicación de este número del Boletín se cumplen diez años consecutivos de este servidor presidir la Junta Editora del Boletín de la Asociación Médica de Puerto Rico y ser responsable de que cada número tuviese artículos de valor científico-médico, que la calidad de la impresión fuese la mejor a nuestro alcance, que tuviese la variabilidad de temas necesarios para interesar a nuestra diversidad de lectores y lo más difícil: que circulase a tiempo. Esto conllevó gran esfuerzo, trabajo y sacrificios; teniendo en cuenta que esta labor hubo que combinarla con una práctica privada de Cardiología Pediátrica muy activa, con un trabajo en el Hospital Pediátrico Universitario y con una familia de 6 personas. Gracias a Dios, a pesar de múltiples obstáculos, la labor encomendada a esta Junta Editora por las Juntas de Directores desde el 1981 se cumplió.

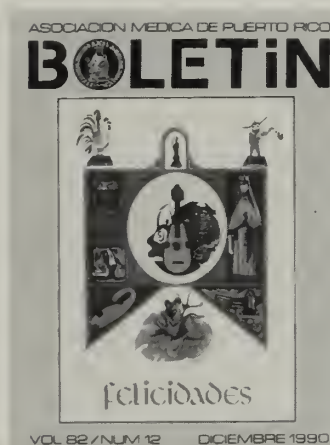
Creemos que ya es tiempo que otra persona continúe con la labor científica-editorial de nuestra Asociación, quizás con nuevas ideas y nuevo entusiasmo como sucedió con nosotros a principios de ésta década. En la Junta Editora actual y en la Asociación Médica en general existe el talento para que el Boletín continúe como hasta el presente; recordando que esta empresa requiere dedicación constante para que pueda tener éxito.

Agradezco a mi Junta Editora el apoyo y colaboración que siempre recibí de todos; los recordaré muy gratamente como excelentes compañeros de trabajo y profesionales íntegros, con dedicación ejemplar por la medicina y por su afán constante de mantener la excelencia científica en nuestra publicación. Al personal de la Asociación Médica que siempre me ayudó con una sonrisa en sus labios a pesar de su sobrecarga de trabajo. A mi más estrecho colaborador, trabajador excepcional y constante defensor de los mejores intereses de la Asociación Médica: Don Primitivo Pagán; sin su ayuda nada de lo logrado en estos diez años hubiese sido posible. A los pasados presidentes y directores, muchas gracias, su apoyo no fue en vano, pues contribuyeron a proyectar la imagen que merece nuestra Asociación. También ayudaron a que el Boletín de la Asociación Médica de Puerto Rico continuase siendo la publicación médica de mayor duración de todas las fundadas en el siglo XX y la de mayor continuidad de todas las publicaciones, incluyendo periódicos, de nuestro país.

Por último: muchas gracias a todos los autores que sometieron manuscritos para publicación; ustedes hicieron la revista. A nuestros lectores: esperamos haber podido mejorar sus conocimientos; ese era nuestro propósito. Creo que cumplí con mi profesión y con mi país, quizás esa fue parte de la encomienda de nuestro Señor al darme la oportunidad de ser médico.

Rafael Villavicencio, MD, FACC  
Presidente Junta Editora  
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Puerto Rico

Diciembre 1990



## Nuestra Portada

Postal Navideña, por David Goitía. El artista nació en San Juan en el año 1932. Desde joven mostró una especial afición por el arte, y careciendo de medios económicos para poder ingresar en una escuela de arte, asiste al taller de arte comercial del maestro Juan Rosado. Allí adquiere los primeros conocimientos en el arte del dibujo y la pintura y logra la oportunidad de conocer algunos de los principales artistas del país. Hacia el 1950 recibe el estímulo de Nino Sparacino, artista italiano que residía en Puerto Rico. Este lo entusiasmó para que continuara sus estudios en Italia, pero su situación económica se lo impide. Conoce en este tiempo al artista español Carlos Marichal, quien toma al joven artista bajo su tutela y lo lleva como estudiante especial a su taller de artes gráficas en la Universidad de Puerto Rico. La influencia del maestro dejó una profunda huella en la formación artística de Goitía.

A fines de la década del '50, Goitía empieza a exponer en diversas galerías del país. En 1958 el Instituto de Cultura Puertorriqueña le otorga una beca para estudiar pintura mural y artes gráficas en México. Estudió bajo los maestros Cangiano, Ocampo y los hermanos Machado a la vez que trabaja como asistente del maestro González Camarena en la pintura de un mural. A su regreso a Puerto Rico, al siguiente año, expone su obra pictórica en la Galería Campeche e inicia su carrera como artista profesional.

Goitía es profesor de la Escuela de Artes Plásticas de Puerto Rico y ha expuesto sus grabados, serigrafías y pinturas en el Instituto de Cultura Puertorriqueña y en las principales galerías del país.

En los últimos años se ha destacado por sus carteles, producidos principalmente para el Instituto de Cultura Puertorriqueña.

La Junta Editora agradece al artista su valiosa colaboración con nuestra revista.

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# ESTUDIOS CLINICOS

## Rendimiento del atleta que hace ejercicio en aire contaminado con ozono

Tomás Morales Cardona, PH.D.

**Resumen:** Se examinó la literatura sobre el rendimiento del que se ejercita en aire con ozono. La acción de ozono está mediada por receptores muscarínicos y otros de naturaleza desconocida localizados, aparentemente, sobre el epitelio respiratorio de transporte gaseoso. Por su acción sobre dichos receptores se reduce la fase inspiratoria de la ventilación pulmonar en un efecto asociado con la aparición de dolor y aumenta la resistencia al paso del aire. Si el ejercicio eleva la ventilación a 90 o más litros por minuto, la concentración efectiva de ozono aumenta hasta potenciar su efecto en la inspiración y la resistencia. La reducción potenciada de la fase inspiratoria y el dolor asociado con ella (a) antagonizan fuertemente el esfuerzo ventilatorio del que se ejercita y (b) reducen la capacidad de responder al aumento en resistencia con inspiraciones aumentadas. De este modo aparece una caída importante en el rendimiento.

El ozono que se encuentra en la atmósfera baja, a nivel de la superficie terrestre, es considerado por algunos autores el contaminante que más daña el rendimiento atlético<sup>1</sup>. Este ozono se forma de la interacción entre la luz solar y el contaminante atmosférico bióxido de nitrógeno. Hay que diferenciar entre el ozono presente en la atmósfera baja y el presente en la atmósfera alta. El ozono en la alta atmósfera se forma de la interacción de la luz solar con el oxígeno molecular, alcanza una concentración de 10 a 100 veces mayor que sobre los terrenos (2.5-10 ppm) y permanece principalmente entre 15 a 25 kilómetros de altura formando la llamada "capa de ozono" (que es motivo de grave preocupación en la actualidad). Este ozono se considera beneficioso porque consume luz ultravioleta solar en su propia formación impidiendo, así, que tan peligrosa radiación alcance significativamente las formas vivas sobre la superficie del planeta.

La revisión más reciente de la literatura sobre el ozono en la superficie terrestre fue la de L.J. Folinsbee en el

1981<sup>2</sup>. Anterior a este autor, Mustafa & Tierney<sup>3</sup> habían revisado el efecto bioquímico y metabólico de concentraciones experimentales de ozono sobre los pulmones de animales vertebrados. Folinsbee revisó el efecto de concentraciones experimentales de ozono similares a las prevalentes en las zonas urbanas sobre la función pulmonar humana. De esa fecha al presente se ha comprendido mejor el efecto nocivo del ozono, sobre todo durante el ejercicio. Este trabajo tiene el propósito de examinar la literatura que explica cómo y por qué se reduce el rendimiento del atleta que respira aire con ozono durante el ejercicio.

### Lugar principal de acción del ozono en los pulmones

El órgano que más sufre el efecto adverso del ozono es el pulmón. En términos del movimiento de aire el pulmón se divide en epitelio de transporte y epitelio de intercambio gaseoso. Por la rapidez de acción del ozono y su baja concentración en las zonas urbanas se cree que su efecto se da principalmente sobre el epitelio encargado del transporte gaseoso y que, incluso en dicho epitelio, no alcanza de manera importante las células subyacentes<sup>3</sup>. El compartimiento de transporte, que se extiende desde la cavidad oral hasta los bronquiolos terminales, es mostrado esquemáticamente en la figura 1 junto al compartimiento de intercambio gaseoso (recuadro). Mustafa & Tierney<sup>3</sup> señalan que el ozono no alcanza de manera significativa el "alveolo distal" que es la parte más lejana, en contacto directo con la sangre, del compartimiento de intercambio gaseoso. Sin embargo, indican que sí alcanza el "alveolo proximal", que es la parte del compartimiento de intercambio más cercana a los bronquiolos terminales; es decir, los alveolos presentes en los bronquiolos respiratorios (fig. 1). Miller, Overton, Jaskot & Menzel<sup>4</sup> señalan que el ozono afecta la zona de contacto entre el epitelio de transporte y el de intercambio; es decir, la zona entre los bronquiolos terminales y los respiratorios, en todos los animales vertebrados estudiados inclusive los seres humanos.

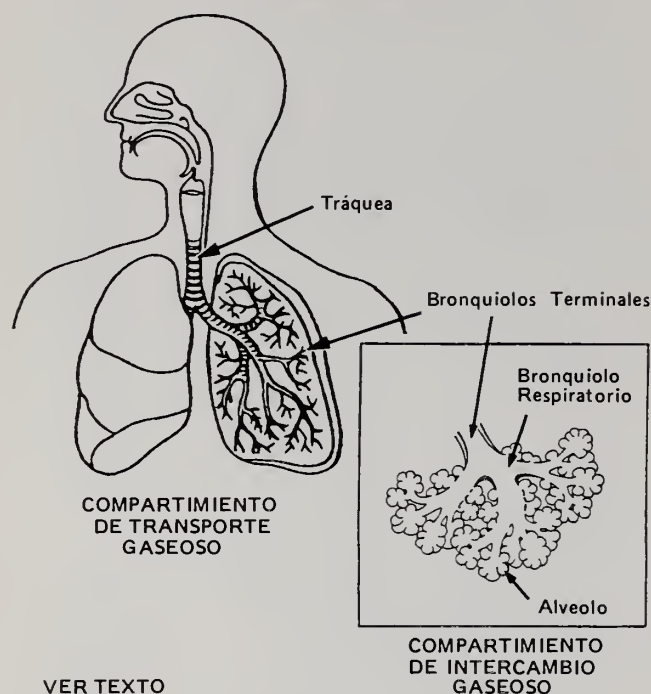
Otro factor que favorece que el efecto de ozono sea principalmente en el comportamiento de transporte lo es el diámetro reducido de los bronquiolos terminales (0.35 a 0.5mm). El ozono podría estrecharlos lo suficiente como para limitar su propio paso hacia el compartimiento de intercambio<sup>3</sup>.

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**FIGURA 1**  
**EL TRACTO RESPIRATORIO HUMANO**



Concluyendo, el ozono parece actuar principalmente a lo largo del epitelio de transporte hasta el comienzo del epitelio de intercambio. Con la ventilación aumentada y respiración oral del ejercicio el ozono puede aumentar aún más su efecto dañino sobre los epitelios de transporte e intercambio proximal. Incluso, puede que penetre más allá de los bronquiolos respiratorios.

#### **Efecto del ozono sobre el epitelio encargado del transporte gaseoso**

En acuerdo con un efecto principalmente en el epitelio de transporte, el ozono altera significativamente las pruebas de función pulmonar que reflejan en gran medida el estado de las vías respiratorias cubiertas por epitelio de transporte. Entre estas pruebas tenemos 1) la resistencia de la vía aérea al paso del aire. 2) el FEV<sub>1</sub> o volumen expulsado forzadamente en el primer segundo. 3) el FVC o capacidad vital forzada 4) el FEF 25-27% o flujo intermedio forzado. Las últimas tres describen el volumen de aire que fluye por los pulmones en una prueba de esfuerzo máximo. Una disminución de ellas indica menores volúmenes de aire, lo que exige mayor esfuerzo ventilatorio para que el oxígeno necesario llegue a los tejidos, sobre todo durante el ejercicio. Veamos primeramente el efecto del ozono sobre la resistencia de las vías aéreas.

#### **Efecto de ozono sobre la resistencia**

La resistencia que ofrecen las vías respiratorias al paso del aire tiene un componente elástico, asociado a la elasticidad natural del sistema, y un componente no-elástico el cual se subdivide en resistencia tisular y resistencia de las vías aéreas<sup>5</sup>.

*Relación entre dosis y respuesta* - McDonnell, Hortsmanm, Hazucha et al<sup>6</sup> estudiaron la relación entre la dosis de ozono y la resistencia de las vías aéreas en 135 sujetos normales divididos en seis grupos. Cada grupo fue expuesto por dos horas y media a una de seis concentraciones entre 0 a 0.4 ppm mientras se ejercitaba a una ventilación de alrededor de 65 litros/min (1/min). La resistencia de la vía aérea aumentó proporcionalmente con la concentración de ozono, incluso en el estándar mismo (0.12 ppm) donde aumentó un 4 por ciento. El aumento en la resistencia aunque exponencial, y significativo a partir de 0.24 ppm de ozono, fue relativamente pequeño alcanzando 37 por ciento a 0.4 ppm de ozono. No obstante, puede ser importante en el momento que el atleta más necesite aire.

Por su parte, Hazucha<sup>7</sup> analizó la relación dosis-resistencia de la vía aérea de seis estudios diferentes informados en la literatura entre 1975 y 1981. Encontró un aumento exponencial de la resistencia que, luego de dos horas de exposición a 0.4 ppm de ozono y una ventilación entre 20 a 45 l/min, fue de 15 por ciento. Hazucha analizó un total de 30 valores de resistencia que representaban 190 individuos que experimentaron 361 exposiciones: 167 en aire libre de ozono y 194 en aire con diferentes concentraciones de ozono.

En 7 de los 30 valores (representando 99 exposiciones) el ejercicio por sí solo, en aire libre de ozono, fue capaz de aumentar la resistencia de la vía aérea. Hubo también 4 valores (68 exposiciones) donde el ejercicio por sí sólo redujo la resistencia. De manera que el ejercicio de por sí altera la resistencia tendiendo más a aumentarla que a reducirla.

En 15 de los valores, que representan 155 exposiciones, la presencia de ozono aumentó la resistencia, lo que quiere decir que en un 80 por ciento de las exposiciones a una ventilación entre 20 a 45 l/min el ozono aumentó dicha resistencia. El que el grupo de McDonnell<sup>6</sup> haya encontrado valores más altos de resistencia que Hazucha<sup>7</sup> bajo condiciones donde sólo la ventilación era bien diferente, sugiere que con ejercicio bien intenso el aumento en resistencia podría ser más grande e, incluso, observarse en más del 80 por ciento de las exposiciones. Es importante señalar que lo que Hazucha clasifica como ejercicio intenso y bien intenso (64 l/min lo considera ya bien intenso) es tan común en atletas de alto rendimiento que no pasa de ser moderado en esta población.

*Modo de acción* - Se ha demostrado por medios farmacológicos que a concentraciones semejantes a las de áreas urbanas el ozono estimula a los receptores colinérgicos muscarínicos<sup>8, 9</sup> ubicados, a juzgar por lo discutido previamente, sobre el epitelio de transporte. Esta estimulación provoca por vía refleja parasimpática la concentración de la musculatura lisa que rodea a bronquios y bronquiolos. El trabajo de Gong, Bodi & Horvath<sup>10</sup>, que demostró que esa broncoconstricción es independiente del sistema simpático beta adrenérgico, es otra prueba de que el sistema nervioso parasimpático es un blanco principal de ozono.

La broncoconstricción tiende a cerrar o a estrechar la vía aérea, lo que aumenta la resistencia al paso del aire. El grupo de Beckett<sup>9</sup> encontró un aumento en resistencia del 49 por ciento en 8 sujetos ejercitándose durante 30



minutos entre 50 a 75 l/min bajo 0.4 ppm de ozono. Estos autores encontraron que el aumento en resistencia producido por el ozono era rápidamente antagonizado por sustancias que relajan la musculatura lisa bronquial, como el agonista beta 2 metaproterenol. Esto sugiere que la resistencia aumentada por el ozono se debe más a la broncoconstricción que a un aumento en las secreciones del tracto respiratorio.

Si bien la broncoconstricción refleja parece ser un mecanismo principal del aumento en la resistencia producido por el ozono, el mecanismo por el cual el ejercicio, por sí mismo, aumenta o reduce la resistencia no es tan bien conocido.

#### Efecto de ozono sobre el FEV<sub>1</sub>, FVC y FEF 25-75%

**Relación dosis - respuesta** - Hazucha<sup>7</sup>, en 24 estudios realizados entre 1964 y 1985 sobre el efecto del ozono durante el ejercicio, calculó la relación entre dosis de ozono y estas tres medidas de función pulmonar. Encontró, primero, que en cada nivel de ejercicio estudiado-clasificados por Hazucha como liviano, moderado, intenso y bien intenso-las tres medidas se reducen significativamente al aumentar la concentración de ozono. En segundo lugar, encontró que la reducción en cada medida individual aumentaba con la intensidad del ejercicio. Para aclarar esto último se preparó la tabla 1 usando datos del FEV<sub>1</sub> extraídos de los gráficos de Hazucha. Puede verse que debido a que cada columna representa la misma concentración de ozono el decremento del FEV<sub>1</sub> observado en cada columna sólo puede explicarse por la intensidad del ejercicio (que es lo único que esta variando.)

Tabla I

Disminución en el FEV<sub>1</sub> con la concentración ambiental de ozono y la intensidad del ejercicio

Ejercicio	Ozono Ambiental en ppm				
	0.0	0.2	0.3	0.4	0.5
Ligero	100%	99	97	94	90
Moderado	100%	98	95	91.5	86
Intenso	100%	97	94	89	83
Bien intenso	100%	95	90	81	71

Modificado de Hazucha MJ (1987)

Recordamos que estos resultados de Hazucha<sup>7</sup> consideran como ejercicio bien intenso ventilaciones que no pasa de ser moderadas en atletas de alto rendimiento. Folinsbee, Bedi & Horvath<sup>11</sup> encontraron en siete atletas de alto rendimiento, durante el ejercicio continuo por 1 hora a 90 l/min, que una concentración de ozono de tan sólo 0.21 ppm producía un decremento en el FEV<sub>1</sub> del 15 por ciento; mucho más que lo que aparece en la tabla 1 a 0.2 ppm. Ejercitándose continuamente por media hora a unos 120 l/min y 0.18 ppm de ozono, Schelegle & Adams<sup>12</sup> encontraron un decremento en el FEV<sub>1</sub> del 5.8 por ciento mientras que Gong, Bradley, Simmons & Tashkin<sup>13</sup> encontraron que ejercicio por una hora, que alcanzó un máximo de 124 l/min en 0.2 ppm de ozono, redujo el FEV<sub>1</sub> en 22 por ciento. Evidentemente, el que se

ejercita a una ventilación de 90 l/min o mayor es más vulnerable al daño de ozono.

**Dosis efectiva** - Los anteriores resultados destacan la importancia de la ventilación sobre el efecto de ozono. La ventilación, junto a la concentración ambiental y el tiempo de exposición, son las tres variables que determinan la concentración efectiva, o "dosis efectiva", que el ozono verdaderamente alcanza sobre el epitelio respiratorio. Puesto que en los anteriores resultados la concentración ambiental del ozono era relativamente baja (0.18 - 0.21 ppm) y el tiempo de exposición relativamente corto (1 hora), se debe concluir que la variable principal en concentrar el ozono sobre el epitelio de transporte y, así, producirse un decremento mayor en el FEV<sub>1</sub>, fue la ventilación. No es lo mismo ventilar 50 litros que 100 por unidad de tiempo.

El tiempo de exposición, por su parte, es la variable menos estudiada. No obstante, recientemente Tilton<sup>14</sup> demostró, comparando resultados de diversos autores, que una concentración ambiental de ozono de tan sólo 0.12 ppm produce un decremento en el FEV<sub>1</sub> similar al que produce concentraciones de 0.20 o más ppm si el que se ejercita a la concentración menor lo hace por 6.6 horas (ejercicio menos intenso durante 50 de cada 60 minutos) en vez de 1 a 2 horas (ejercicio más intenso durante 30 de cada 60 minutos). Los anteriores hallazgos sobre ventilación y tiempo de exposición indican que la concentración ambiental no es la variable de mayor peso en el efecto de ozono sobre la función pulmonar. Es útil mostrar en forma de tabla el resumen de Tilton<sup>4</sup> sobre las concentraciones ambientales de ozono que reducen el FEV<sub>1</sub> promedio de un grupo de sujetos en diversos tipos de actividad durante estudios de dos horas de duración (tabla 2).

Tabla II

Concentraciones ambientales de ozono que reducen el FEV<sub>1</sub> por tipo de actividad

Ozono Ambiental en ppm	Actividad	Intensidad del Ejercicio
0.5	Reposo	Ninguno
0.37	Caminar lento	Liviano
0.30	Caminar rápido	Moderado
0.24	Correr	Intenso
0.18	Correr competitivamente	Bien intenso

Modificado de Tilton BE (1989)

**Modo de acción** - Para examinar cómo es que el ozono reduce el FEV<sub>1</sub>, FVC y FEF 25-75% es útil recordar que el FEV<sub>1</sub> y FEF 25-75% son indicadores de enfermedades obstructivas mientras que el FVC lo es de enfermedades restrictivas. La obstrucción se refiere más a cambios locales en las vías aéreas siendo la resistencia la medida por excelencia para detectar obstrucción. La restricción se refiere a cambios más amplios de naturaleza sistémica siendo el FVC una buena medida para detectar restricción.

Puesto que el ozono reduce el FEV<sub>1</sub>, FVC y FEF 25-75% se debe concluir que produce cambios tanto de naturaleza obstructiva como restrictiva y en cada caso, debe actuar por mecanismos diferentes ya que la obstrucción y restricción constituyen patologías diferentes. Así lo confirma el trabajo del grupo de Beckett<sup>9</sup> que encontró que el mecanismo que aumenta la resistencia de la vía aérea (la medida por excelencia de obstrucción) es diferente del que reduce el FVC. McDonnell y su grupo<sup>6</sup> encontraron que el efecto del ozono sobre la resistencia no está correlacionado estadísticamente con el efecto sobre el FVC. Sí encontraron, en cambio, que el efecto sobre el FEV<sub>1</sub> y FEF 25-75% está correlacionado con su efecto sobre el FVC, lo cual interpretan como que el FEV<sub>1</sub> y FEF 25-75% son reducidos por más de un mecanismo.

De manera que la irritación del ozono produce cambios que tanto obstruyen como restringen el paso del aire. El principal mecanismo de los efectos obstructivos parece ser el mecanismo reflejo parasimpático que eleva la resistencia de la vía aérea por medio de una broncoconstricción. Pero hay otros mecanismos activados por el ozono que contribuyen a la obstrucción, tales como (a) aumento en las secreciones, (b) inflamación tisular, (c) reducción del umbral broncoconstrictivo de la histamina y acetilcolina y (d) aumento en los metabolitos broncoconstrictores derivados del ácido araquidónico<sup>15</sup>. En vista de la mayor vulnerabilidad del que se ejercita bien intensamente todos estos efectos deben considerarse como importantes.

Por su parte, la manera por la que se produce la restricción es menos conocida. Se especula que el ozono irrita ciertos receptores sobre el epitelio respiratorio - lo más seguro epitelio de transporte - que deprimen, o inhiben, el esfuerzo inspiratorio de la persona ya sea involuntaria o voluntariamente por incomodidad<sup>6</sup>. Recientemente se ha informado acerca de la existencia de dichos receptores. Hazucha, Bates & Bromberg<sup>16</sup> han mostrado que el ozono parece estimular receptores sensibles a la lidocaína, sobre las vías aéreas humanas, que producen una inhibición involuntaria de la inspiración. Al disminuirse el esfuerzo inspiratorio se reduce la capacidad total de los pulmones y, así, el FVC. Deben aquí puntualizarse dos cosas: primero, que la reducción de la inspiración está asociada con la aparición de dolor que debe originarse en la irritación, o lesión, que produce el ozono sobre el epitelio respiratorio. Segundo, al reducir la inspiración el ozono antagoniza el esfuerzo ventilatorio del que hace ejercicio.

Otros efectos importantes de ozono en el que se ejercita son: aumento en la frecuencia respiratoria (por encima de la asociada con el ejercicio), reducción en el volumen corriente en reposo y tos.

#### **Efecto del ozono sobre el epitelio encargado del intercambio gaseoso**

No es indispensable postular un efecto del ozono sobre el epitelio de intercambio para tenerse ya una acción importante a través del epitelio de transporte. No obstante lo anterior, el ejercicio favorece una penetración más profunda del ozono en el compartimiento de inter-

cambio gaseoso por que eleva significativamente la presión de aire en las vías de transporte. Además, durante el ejercicio bien intenso el tiempo que tienen los glóbulos rojos para saturarse de oxígeno, en su veloz paso a lo largo de la membrana de intercambio, se reduce de 0.7 a 0.3 segundos (incluso a menos en algunas zonas pulmonares). Durante el ejercicio intenso se está al borde de que no llegue suficiente oxígeno a la sangre arterial, de manera que puede que no haga falta tanto ozono ni tiempo de exposición para que afecte el epitelio de intercambio y reduzca la oxigenación arterial de manera detectable.

#### **Efecto del ozono sobre la oxigenación arterial**

Lo cierto parece ser, sin embargo, que ni bajo ejercicio bien intenso el ozono alcanza de manera generalizada los alveolos pulmonares. Hemos identificado tan sólo tres trabajos en la literatura sobre el efecto del ozono en la oxigenación arterial durante el ejercicio, que sugieren un efecto limitado o ausente. Nieding & Wagner<sup>17</sup>, en Alemania, detectaron una reducción significativa (de 7 mm de Hg) en la oxigenación arterial de sujetos saludables durante el ejercicio intermitente mientras respiraban 0.1 ppm de ozono por dos horas. Sin embargo, cuando el ozono fue administrado combinadamente con SO<sub>2</sub> y NO<sub>2</sub> se produjo una reducción similar, lo que sugiere falta de especificidad en el resultado<sup>1</sup>. Linn, Jones, Bachmayer, et al<sup>18</sup> en los Angeles, repitieron las condiciones de trabajo de Nieding & Wagner y no detectaron cambios significativos en la oxigenación arterial a 0.2 ppm (la concentración se duplicó para minimizar la adaptación o baja reactividad que exhiben los residentes de esa ciudad a ozono). Por último, Holub, Morgan, Frank et al<sup>19</sup> encontraron una reducción moderada, del 3.7 por ciento, en la oxigenación arterial pero por menos de un minuto de duración y no aparecía en todos los períodos de ejercicio.

En fin, no hay pruebas uniformes de que el ozono tenga efecto adverso significativo sobre el epitelio de intercambio gaseoso. Mustafa & Tierney<sup>3</sup> señalan que al nivel de los bronquiolos respiratorios, al comienzo del compartimiento de intercambio, el ozono daña las células alveolares de tipo I en animales de laboratorio, que son rápidamente sustituidas por las más resistentes de tipo II que eventualmente se transforman en tipo I. Pero aparentemente este daño no se traduce en una oxigenación arterial reducida, lo que podría explicarse tanto por la poca contribución de los bronquiolos respiratorios a la oxigenación arterial como por un efecto protector de las células de tipo II. Todo parece indicar que las causas que impiden que el ozono invada de forma generalizada el compartimiento de intercambio (alta reactividad, concentraciones ambientales bajas y otras) son efectivas la mayor parte de las veces.

#### **Efecto del ozono al nivel molecular y tisular**

Se cree que el efecto de ozono se basa en su potente acción oxidante que al quitarle electrones y/o hidrógenos a las moléculas componentes de la membrana celular irrita e, incluso, puede dañar dicha membrana<sup>3</sup>. La



oxidación directa producida por el ozono en su forma de  $O_3$  no es tan dañina como la indirecta. Mientras que en la directa una molécula de ozono oxida sólo una molécula celular, en la indirecta oxida a varias. Esto se debe a que el oxígeno atómico, que surge de la descomposición del ozono en los tejidos vivos a oxígeno molecular y oxígeno atómico, lleva a la formación de radicales libres que también son potentes agentes oxidantes<sup>3</sup>. Así, el ozono, que es de por sí oxidante, produce indirectamente compuestos igualmente oxidantes que amplifican su efecto adverso. Los efectos de ozono sobre los tejidos vivos son muy parecidos a los de la radiación, que actúa indirectamente por medio de la formación de radicales libres. Como ejemplos de los efectos oxidantes al nivel molecular tenemos (a) la peroxidación de los enlaces dobles de los ácidos grasos insaturados que abundan en las membranas biológicas, (b) oxidación de los grupos sulfhidrilos de las proteínas de la membrana y (c) disminución de la actividad de enzimas ligados a la membrana celular<sup>3</sup>.

Con un área de epitelio respiratorio entre 60 a 80 metros cuadrados, los pulmones del adulto ofrecen una superficie de membrana enorme que se expone a la acción irritante del ozono. No es de extrañar, pues, que los efectos del ozono sobre el tejido pulmonar humano parezcan deberse, como bien señalan Mustafa & Tierney<sup>3</sup>, casi enteramente a las consecuencias de dicha irritación. Como ejemplo de los efectos del ozono al nivel tisular pulmonar tenemos inflamación, hipersecreción y broncoconstricción<sup>15</sup>. No se sabe si el ozono produce daño permanente que lleve el desarrollo de bronquitis, enfisema o malignidad en humanos<sup>3</sup>.

### Niveles de ozono en el aire de Puerto Rico

En Puerto Rico se detectan valores de ozono que no están tan lejanos a los de Los Angeles. La figura 2A muestra los valores máximos mensuales de ozono que registran en las dos estaciones de muestreo que mantiene el Gobierno de Puerto Rico. La figura 2B, por su parte, nos permite comparar una curva estacional típica de Los Angeles con Levittown, en Toa Baja, Puerto Rico. Mientras que en Los Angeles las concentraciones mayores de ozono se registran en el verano - cuando más abunda la luz solar - y las menores en el invierno, en Puerto Rico fluctúan debido a que la cantidad de luz solar no varía tanto por estación. El gráfico de Levittown de 1983 indica que en Los Angeles la concentración máxima se registra temprano en la tarde mientras que en Puerto Rico se da tarde en la mañana. En el gráfico de Levittown

### OXONO EN PUERTO RICO

#### A. PROMEDIOS DE 1 HORA: VALORES MAXIMOS POR MES

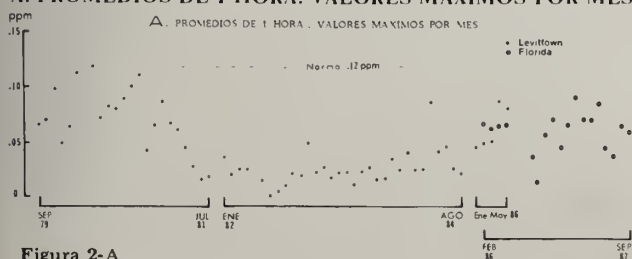


Figura 2-A

#### B. PROMEDIOS DE 1 HORA: VALORES POR HORA DEL DIA POR ESTACION DEL AÑO

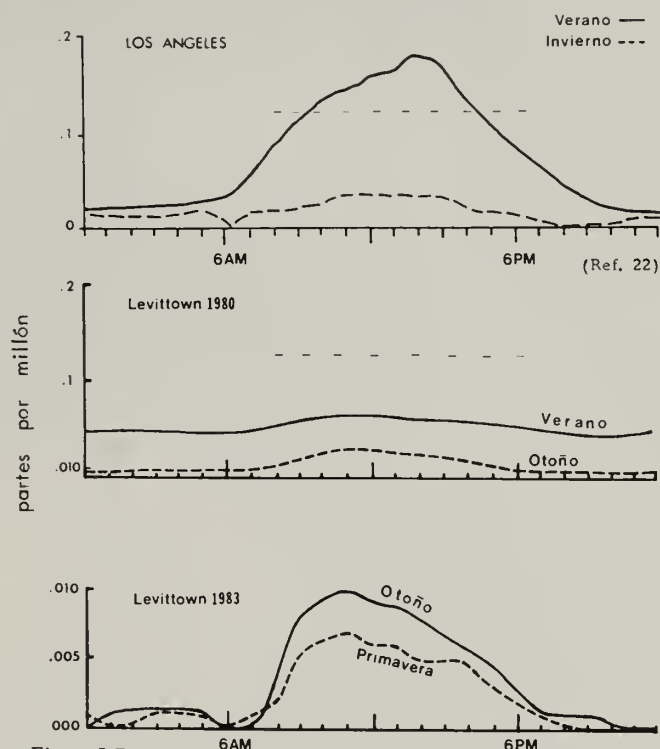


Figura 2-B

de 1980 se puede ver que las concentraciones de ozono entre 8 de la noche y 6 de la mañana pueden ser más altas en Levittown que en Los Angeles.

### Discusión y Conclusiones

Mientras el ejercicio eleva la ventilación, el ozono reduce la fase inspiratoria de la misma - un efecto restrictivo - y, simultáneamente, cuando más aire se necesita el ozono interfiere con su paso al aumentar la resistencia de las vías respiratorias - un efecto obstructivo. Ambos efectos parecen estar mediados por receptores localizados en mayor cantidad, probablemente, sobre el epitelio de transporte gaseoso. Mientras que el efecto obstructivo es mediado por receptores muscarínicos, el restrictivo lo es por receptores de naturaleza menos conocida pero sensibles al anestésico local lidocaína. Esto último sugiere la posibilidad de que haya alguna relación entre el efecto del ozono sobre la inspiración y el dolor asociado con ese efecto. Actualmente se cree que dicho dolor se origina en la lesión (o irritación) que el ozono produce sobre el epitelio respiratorio<sup>20</sup>.

Cuando se respira ozono durante el ejercicio se está, pues, bajo condiciones donde el gas antagoniza el esfuerzo ventilatorio en una acción asociada con la aparición de dolor y reduce la capacidad de responder al aumento en resistencia con inspiraciones aumentadas. Creemos que si tales condiciones se potencia, podrían explicar el por qué ozono reduce el rendimiento del atleta.

Recordamos, en primer lugar, que el trabajo de Hazucha<sup>7</sup> demostró el efecto potenciador de la inten-

sidad del ejercicio sobre el efecto de ozono en la función pulmonar. Simultáneamente Gong, Bradley, Simmons & Tashkin<sup>13</sup> encontraron que a 0.20 ppm de ozono 6 de 17 ciclistas de nivel internacional sufrieron limitaciones en su rendimiento durante ejercicio submáximo a un promedio de 90 l/min; i.e., no pudieron terminar los 60 minutos previstos de ejercicio submáximo. Cuando el ejercicio (siempre a 0.20 ppm de ozono) se elevó al máximo, a una ventilación de 125 l/min, 13 de 17 ciclistas sufrieron limitaciones en su rendimiento; i.e., cayeron al límite previsto de pedaleo de 75 revoluciones por minuto (rpm) en menos tiempo que en aire sin ozono. En promedio, el grupo de los 17 cayó a 75 rpm 30 por ciento antes del tiempo que cayó en aire sin ozono. Paralelamente, el grupo experimentó un decremento del 18 por ciento en la ventilación máxima promedio (de 152 a 124 l/min.) y de 16 por ciento en el consumo máximo de oxígeno.

Creemos que los anteriores resultados sugieren que el ejercicio bien intenso (sobre los 90 l/min.) eleva la dosis efectiva de ozono que llega al epitelio respiratorio hasta potencial su efecto sobre la inspiración y la resistencia a niveles que limitan la actividad humana. Trabajos como los de Wayne, Wehrle & Carroll<sup>21</sup> y Schelegle & Adams<sup>12</sup> informan también de una caída en el rendimiento asociada con concentraciones ambientales de ozono bajas y ejercicio bien intenso. En los trabajos del grupo de Gong<sup>13</sup> y el de Schelegle<sup>12</sup>, además de niveles bajos de ozono y ejercicio bien intenso hubo períodos de exposición relativamente breves (1 hora).

Según Folinsbee & Raven<sup>20</sup>, el efecto de ozono sobre la inspiración y el dolor que lo acompaña se considera un factor más importante en la caída en rendimiento que su efecto obstructivo. Como señalan estos autores, al limitarse la ventilación se limita el consumo máximo de oxígeno y el rendimiento atlético máximo. De acuerdo a Gong, Bradley, Simmons & Tashkin<sup>13</sup> el rendimiento puede caer significativamente a una concentración ambiental de ozono entre 0.12 a 0.20 ppm (recordamos que 0.12 representa la norma).

De los resultados discutidos se confirma un principio importante en el ejercicio y el deporte de la segunda mitad del siglo 20: el ejercicio potencia, o aumenta, el daño de la contaminación.

**Abstract:** The literature on the performance of those exercising in air containing ozone was examined. The action of ozone is mediated by muscarinic receptors and others of unknown nature localized, apparently, over the respiratory epithelium of gaseous transport. Due to its action on those receptors the inspiratory phase of the pulmonary ventilation is reduced in an effect associated with pain and, simultaneously, the resistance to the pass of air is increased. If exercise increases ventilation to 90 or more liters per minute the effective dose of ozone increases potentiating its effect on the inspiration and the resistance. The potentiated reduction of the inspiratory phase and the associated pain (a) strongly antagonize the ventilatory effort of exercise and (b) reduced the capacity of response to the increase in resistance with augmented inspirations. In this way an important decrease in performance appears.

## Reconocimiento

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# AIDS Risk Behavior Patterns Among Intravenous Drug Users in Puerto Rico and the United States

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**Abstract** We interviewed 385 IV drug users recruited in the streets of the San Juan metropolitan area and compared our findings with comparable results from projects in the United States. As expected, intravenous (IV) drug users, irrespectively of the race or ethnic group they belong to or the geographical setting in which they live, are still practicing HIV risk behaviors. Overall, IV drug users in this analysis are young, however, both Puerto Rican and Hispanic groups have completed less years of school than Blacks and Whites in the United States. The fact that almost half of Puerto Rican IV drug users in the United States reported illegal activities as a source of income surprised investigators. However, as hypothesized by investigators, almost half of the Island's IV drug users reported to live with parents. Puerto Rican IV drug users are still practicing HIV risk behaviors, they inject drugs and use shooting galleries to inject drugs more frequently, and are less likely to clean needles and use condoms than Puerto Ricans in the U.S., Blacks and Whites. It is a well known fact that intravenous drug users are the largest group at risk for the acquired immunodeficiency syndrome (AIDS) in Puerto Rico and among Puerto Ricans in the United States. IV drug users are also the major risk for heterosexual transmission and main source of perinatal transmission of the disease. Thus, resources for preventing AIDS in Puerto Rico are needed most among IV drug users, where 44.5 of the subjects in this study are HIV positive.

addicts in metropolitan areas in Puerto Rico is similar to New York, which is considered to have one of the highest rates of drug abusers among US cities. García and Colón estimate that for 1977-79 Puerto Rico had 13,703 addicts; by 1980-82, 28,388, for 1983, 33,795 and by the years 1985-87 the number came to 37,703 addicts; by 1980-82, 28,388, for 1983-85, 33,795 and by the years 1985-87 the number came to 37,595, and annual average increase rate of 11% (García and Colón, 1989) (Table 1).

**Table 1**  
Estimate of drug abuse prevalence in Puerto Rico  
for selected drugs, years 1977 to 1987

Drugs of abuse	Periods			
	1977-78-79	1980-81-82	1983-84-85	1985-86-87
Marihuana	9,674	22,494	28,110	18,140
standard error*	2,519	5,856	7,315	4,720
Cocaine	†	†	†	15,328
standard error				3,989
Heroin	4,029	5,894	5,685	4,127
standard error	704	1,030	994	721
All of the above	13,703	28,388	33,795	37,595
standard error	2,615	5,946	7,382	6,222

\* 95% confidence level

† No estimate possible for these periods

SOURCE: García and Colón, 1989.

Puerto Rico has the second highest rate of reported AIDS cases among United States' cities, 48.11 per 100,000 population (CDC, 1990). Only Washington, D.C. reports a higher prevalence. While homosexuality constitutes the largest risk factor for the spread of the Human Immunodeficiency Virus (HIV) in the Mainland, in Puerto Rico IV drug use is the most important risk factor. In Puerto Rico, the number of drug abusers is increasing 13 times faster than the population increase and, according to the latest estimates, concentration of

Puerto Ricans are the Hispanic group with highest incidence of AIDS among U.S. Hispanic groups. Selik and colleagues report that in each region in the United States the cumulative incidence of AIDS was greater among Puerto Rican born persons than persons born in Cuba, Mexico or other Latin American countries. These scientists argue that in the nation as a whole, Puerto Rican born persons were the only Latin American born persons in which most AIDS cases were heterosexual IV drug users (Selik et al, 1989).

Risk factors and basic knowledge related to HIV transmission have been available relatively fast since the disease was identified in 1981. By 1983 the causative agent of AIDS, the Human Immunodeficiency Virus (HIV) was discovered. The availability of diagnostic assays for antibodies to HIV, since 1985, have led gradually to a more clear picture of the extent and

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distribution of the disease. Further, more epidemiologists have been able to detect the modes of transmission of the virus. Sex, blood and mother to child transmission are the universal modes of transmission. The epidemiologic evidence for transmission of human immunodeficiency viruses through body fluids is conclusive. Sharing of infected needles in particular, has consistently been reported as the behavior most strongly associated with HIV infection among IV drug users. Exchanges of sex for drugs or money prevail among IV drug users, behaviors which might also place them at risk of HIV infection.

The Puerto Rico AIDS Prevention Project (PRAPP) is the only project in the Island specifically designed to ascertain under what circumstances specific intervention strategies are effective in changing those risk behaviors that place IV drug users not in treatment at risk of getting infected with HIV. The Puerto Rico AIDS Prevention study is being conducted by the Research Institute of the Department of Anti-Addiction Services and the Department of Health of the Municipality of San Juan. Funded and monitored by NIDA since October, 1988, the study involves IV drug users not in treatment recruited from social settings with the largest prevalence of IV drug use in metropolitan San Juan. PRAPP is one of the projects funded and monitored by NIDA in 63 sites in continental USA, including Hawaii and Puerto Rico. In addition to data on HIV seroprevalence, PRAPP provides detailed information about sociodemographic characteristics, including various lifetime periods of incarceration, patterns of drug injection and risk behaviors for HIV infection. In this analysis we take the opportunity provided by this data set and comparable data set from similar projects in the United States in order to examine the difference between ethnic groups of IV drug users with respect to high risk behaviors and lifestyles. Our ultimate goal is to identify types of risk behaviors prevalent among these groups so as to provide health educators and other health professionals the empirical information required to design intervention programs to reduce risk behaviors and arrest the transmission of HIV.

## Methods

The study population of the Puerto Rico AIDS Prevention Project, 385 IV drug users recruited in the streets of the San Juan metropolitan area, provided the data for this analysis. Outreach workers recruited study participants from the streets of different communities known to have high prevalence of IV drug use. The criteria for selection was current involvement in drug injection and absence of participation in drug treatment programs during the previous thirty days. Sampling bias is always a problem in studies of IV drug users. It is obviously not possible to draw a probability sample of IV drug users since a complete sample frame can not be constructed. It is well known that no one understands the magnitude or basic characteristics of the IV drug user population in Puerto Rico. Therefore, to obtain a sample that would at least provide representation from varied segments of the study population we recruited subjects through a diversity of sources. Outreach workers ap-

proached IV drug users, directly as well as indirectly, through use of the social network. Those who consented to participate in the study were taken to assessment centers and provided counseling prior to their blood test. HIV antibody status was ascertained by enzyme immunoassay (ELISA). Specimens found to be positive were confirmed by a Western Blot test and reported as positive when both test results were positive. All participants received counseling before and after results were offered.

Sociodemographic and behavioral data were gathered by trained interviewers using the AIDS Initial Assessment (AIA) questionnaire. This structured interview was designed by the National Institute on Drug Abuse and the NOVA Research Company to collect information on the National AIDS Demonstration Research (NADR) and AIDS Target Outreach Models (ATOM) projects. The AIA was translated into Spanish and revised in Puerto Rico to make it more comprehensible to local IV drug abusers. Data were also collected on participants' history with treatment programs, incarceration, and travel to other U.S. cities. Information on participants' drug injection and sexual practices, including frequency and patterns of these behaviors during the six months prior to the interview, were also collected. Participant observation notes and transcribed conversations collected by the outreachers provide valuable qualitative data for this analysis. Data from IV drug users in the Mainland was collected by all the other NADR projects and submitted to us through NOVA Research Company.

## Findings

Participants of the PRAP Project, similar to participants of the same type of studies in the Mainland are young. Almost 60% of the island's IV drug users are less than 35 years old, while 68% of the Mainland Puerto Ricans, 63.4% Other Hispanics, 43.5% Blacks and 62.8% Whites are less than 35 years old (Table 2). More than half of the Islanders, 64.2% of the Puerto Ricans in the Mainland, and 63.7% Other Hispanics report they have not completed high school. This rate is much less for both Blacks and Whites, about 35% (Table 2).

Islanders (43.4%) and Other Hispanics (28.8%) are slightly more likely to live with parents than other ethnic groups in the continent, 8.5% Whites, 14.2% Blacks and 17.0% Mainland Puerto Ricans. However only 23.1% of Islanders and 20.4% of Mainland Puerto Ricans report they live with sex partners; 28.9% Other Hispanics, 20.4% Whites, and 23.5% Blacks (Table 2).

Employment and welfare are the main sources of income reported by Islanders, 26.5 and 22.4% respectively. Only 17.5% of Mainland Puerto Ricans report a job as a source of income, while Other Hispanics report 30.5%, 26.5% Blacks and 29.6% Whites. However, 49.8% of Mainland Puerto Ricans report illegal activities as a source of income, much higher than Whites, who report 31%, Other Hispanics 26%, Blacks 24.7% and Islanders 17.0% (Table 2).

A substantial number of IV drug users in the Mainland report they have been in prison, Mainland Puerto Ricans

78.4%, Other Hispanics 87.5%, Blacks 83.9% and Whites 85% (Table 2). A lower percent of Islanders have ever been incarcerated, 65.6%. Also, 70% of both Islanders (69.8%) and Mainland Puerto Ricans (70.0%) have utilized drug treatment programs, followed, with similar high percentages, by Whites (63.2%), Blacks (56.0%), and Other Hispanics (53.9%) (Table 2). Islanders, similar to all other groups in the continent start their drug injection career between ages 16 y 18.

**Table 2**  
Sociodemographic characteristics of IV DU's  
by race/ethnicity and place of recruitment\*

	Island		Mainland		
	Puerto ricans	Puerto ricans	Other Hispanic	Blacks	Whites
<i>Age:</i>					
24	15.1	13.4	17.0	4.9	15.1
25-34	44.6	54.7	46.4	38.6	47.7
35-44	34.2	27.8	24.0	44.2	30.1
45-54	5.5	3.5	9.5	10.0	6.1
55	0.5	0.6	3.1	2.3	1.0
n †	383	879	1426	4967	2212
<i>Schooling:</i>					
High					
School	56.3	64.2	63.7	35.3	34.5
High					
School	27.9	24.9	29.3	42.0	42.9
High					
School	15.9	10.8	7.0	22.7	22.7
n	384	878	1426	4961	2207
<i>Major</i>					
<i>Source of</i>					
<i>Income:</i>					
Job	26.5	17.5	30.5	26.2	29.6
Welfare	22.4	14.3	15.6	23.7	13.5
Illegally	17.0	49.8	26.1	24.7	31.0
Other	34.1	18.3	27.8	25.4	25.9
n	370	747	1228	4107	1959
<i>Living</i>					
<i>With:</i>					
Alone	17.7	29.8	14.7	30.4	27.0
Sexual					
Partner	23.1	20.4	28.9	23.5	29.4
Parents	43.4	17.0	28.8	14.2	8.5
Other	28.1	40.7	41.9	40.8	45.3
n	384	879	1426	4967	2212
<i>Ever Been:</i>					
<i>Drug</i>					
<i>Treatment</i>					
Jail/	69.8	70.0	53.9	56.0	63.2
Prison	65.6	78.4	87.5	83.9	85.0
n	384	877	1425	4959	2212

\* percentage distributions

† n values might vary due to missing responses

### Risk behaviors

The fact that 20.5% of Island IV drug users participating in the Puerto Rico AIDS Prevention Project report having used crack was a surprise to investigators.

Also surprising is the large number of Puerto Ricans in the Mainland that report using crack, 55.6% (Table 3). As Table 4 shows, a higher proportion of both groups of Puerto Ricans inject drugs daily: 84.9% Islanders, 79.6% Mainland Puerto Ricans, 61.9% Other Hispanics, 49.8% Blacks and 48.8% Whites. However, a lower percent of Islanders rent or borrow needles: Islanders 49.6%, followed by Blacks, 52.2%, Mainland Puerto Ricans, 56.1%, and Whites 63.4%. It is worth noting that other Hispanics report more renting or borrowing needles than any other of their IV drug peers in Puerto Rico or the continent, 68.5% (Table 4).

**Table 3**  
Drugs ever used by race/ethnicity and place of recruitment\*

	Island		Mainland		
	Puerto ricans	Puerto ricans	Other Hispanic	Blacks	Whites
Crack	20.5	55.6	30.8	66.2	59.6
IV					
Cocaine	91.9	55.6	30.8	66.2	59.6
IV					
Heroin	96.1	97.1	96.9	90.0	88.9
IV					
Speedball	98.6	91.1	70.6	85.7	78.7
n	385	878	1424	4963	2210

\*n percentage distribution

**Table 4**  
Percent of IV DU's who have engaged in drug injection risk  
behaviors by ethnicity and place of recruitment\*

	Island		Mainland		
	Puerto ricans	Puerto ricans	Other Hispanic	Blacks	Whites
<i>Daily</i>					
<i>Injection</i>					
<i>Needles</i>					
Borrowed	84.9	79.6	61.9	49.8	48.8
or rented	49.6	56.1	68.5	52.2	63.4
Never					
Bleached	52.9	43.1	55.1	38.9	37.6
Always					
New	23.4	15.9	20.50	22.9	14.0
<i>Shared</i>					
<i>Cookers</i>	81.3	75.1	78.0	70.7	77.3
Rinse					
Water	58.6	63.3	74.7	60.3	66.7
n	385	872	1529	4929	2186

\* percentage distribution

Islanders tend to look more to Puerto Ricans in the Mainland than any other group in the United States in terms of the proportion reporting shooting half the time or more at their own place, friends' places, social gatherings and dealers' places (Table 5). Worth noting is that a substantial number of Puerto Rican IV drug users use shooting galleries to inject drugs half the time or more, 64.3%, followed by Puerto Ricans in the Mainland with a much lower percentage, 27.9% (Table 5). Also



**Table 5**  
Social settings where IVDU's report shooting drugs half the time or more by race/ethnicity and place of recruitment\*

	Island	Mainland			
	Puerto Ricans	Puerto Ricans	Other Hispanic	Blacks	Whites
Own Place	42.9	40.5	60.9	57.0	63.5
Friend's Place	31.7	29.1	44.9	42.3	35.6
Social Gathering	3.4	4.8	11.8	8.3	9.9
Dealer's Place	8.9	7.1	16.0	10.4	15.1
Shooting Gallery	64.3	27.9	16.9	17.6	10.4
Abandoned building	18.8	26.0	17.6	14.2	10.1
Street	11.2	14.2	22.9	8.3	12.8
n	385	874	1529	4920	2189

\* percentage distribution

worth noting is that only a minority of the Islanders often share needles with sex partners: Islanders 7.3%, Mainland Puerto Ricans 15.4%, Other Hispanics 23.8, Blacks 29.2% and Whites 35.7% (Table 6). Furthermore, a substantial number of both Islanders and Puerto Ricans in the Mainland report the highest rate of often shooting drugs alone; 65.6% and 67.8% respectively. Other Hispanics tend to share needles more often with friends, 34.7%, and running partners, 41.9%, than any of the other groups (Table 6). Although Islanders claim not to share needles as frequently as the other groups of IVDU's, they share the cooker with other peers at a higher rate, 81.3% report they frequently practice this behavior followed by other Hispanics, 78.0% and Whites, 77.3% (Table 4). Islanders and Other Hispanics are less likely to clean needles with bleach in the last six months than any other group; 53% and 55.1% respectively (Table 4). It is worth noting that Island Puerto Ricans 23.4%, and Blacks 22.9% are more likely to have always used new needles during the past six months than Mainland Puerto Ricans,

**Table 6**  
Needle sharing half the time or more by race/ethnicity and place of recruitment\*

	Island	Mainland			
	Puerto Ricans	Puerto Ricans	Other Hispanic	Blacks	Whites
Sex					
Partner	7.3	15.4	23.8	29.2	35.7
Running Partner	14.3	23.7	41.9	31.0	32.7
Friends	16.7	18.3	34.7	20.1	23.3
Strangers	4.2	6.0	6.9	3.6	3.9
No One	65.6	67.8	60.3	56.8	51.5
n	385	864	1528	4916	2183

\* percentage distribution

15.9%, Other Hispanics, 20.0% and Whites 14.0% (Table 4). Islanders (37.0%) and Mainland Puerto Ricans (25.1%) are more likely to report that they didn't have sexual partners during the last six months than Other Hispanics 12.6%, Blacks 10% and Whites 14.1%. Other Hispanics, with 80.3%, and Islanders, with 73.6% are the most likely not to have used a condom during the last six months. Mainland Puerto Ricans, 57.9%, are closer to Whites, 62.0%, and Blacks, 63.4% in this behavior (Table 7).

Although we do not have the statistics to compare our participants with their peers in the United States, in the Island 46.3% of the Puerto Rico AIDS Prevention Project's participants are HIV positive.

**Table 7**  
Sex risk behavior of IVDU's by race/ethnicity and place of recruitment\*

	Island	Mainland			
	Puerto Ricans	Puerto Ricans	Other Hispanic	Blacks	Whites
Sexual Partners					
None	37.0	25.1	12.6	10.0	14.1
One	38.0	33.2	48.9	35.0	32.4
Two or More	25.0	41.6	38.4	54.9	53.5
n	374	878	1426	4963	2207
Have Not Used Condoms	73.6	57.9	80.3	63.4	62.0
n†	242	657	1246	4465	1896

\* percentage distribution

† Percentages calculated based on number of subjects indicating at least one sexual partner.

## Summary and Interpretation

As expected, the prevalence of HIV infection among the IV drug user population is significantly high, a fact that should be of great concern to health professionals, drug treatment officials, policy makers and all Island citizens. Puerto Rico has the sociostructural circumstances that facilitate the spread of HIV infection and AIDS. The Island is small with closely knitted primary relations, a high rate of divorce and consequently a high rate of single young women and men looking for second sex partners. There is a high rate of sterilization (Vázquez, 1987), therefore, a great number of young women do not use family planning services where they can be helped to prevent sexually transmitted diseases, including AIDS. Most important of all, Puerto Ricans are closely tied to large cities in the United States where AIDS is highly prevalent. Our continuous contact with the Mainland through circular migration, places New York, Chicago, New Jersey, Philadelphia and Puerto Rico's populations in close and continuous interaction, exchanging not only types of cultural patterns like language, music, dancing

and food, but also communicable and sexually transmitted diseases such as AIDS.

The fact that 20.5% of the participants of the project reported having used crack surprised investigators as it is a common belief among policy makers that crack has not entered the drug market in Puerto Rico. Data from the U.S. shows that Puerto Ricans in the Mainland have also used crack. Therefore, epidemiologists and drug treatment personnel must closely watch the prevalence and patterns of use of this new drug in Puerto Rico, as in the U.S. crack users are heavily involved in illegal activities and HIV sex risk behaviors.

Puerto Rican IV drug users are young, as all other participants in the IV drug users AIDS projects in the Mainland. Much to the surprise of investigators, Mainland Puerto Ricans have the highest rate of illegal behavior as a source of income among all other IV drug user groups in the Mainland. Hispanics' familism is evident among IV drug users; in both Islander and Other Hispanic groups, a large number of individuals report living with their parents. The fact that a much lower percentage of Puerto Rican IV drug users in the Mainland report living with the family than other Hispanics might mean that they are more recent migrants and that their families are still in the Island. The interaction between not living with parents, not having sex partners, living alone, not having a job or government assistance provides the setting for social isolation, less social integration and more scarcity of money for Puerto Ricans in the Mainland. Exploring the relationships of these variables with the illegal behavior among this population would help us to understand the relationship between IV drug use and crime.

The high frequency of drug injection in shooting galleries in Puerto Rico might be associated with the high rate of HIV seropositivity among this population. However, the lower rate of needle sharing, more frequent use of new needles reported by Island Puerto Ricans, is not consonant with their higher frequency of injection. It may very well be that drug craving does not facilitate reduction of needle injection. Changing this physiological craving has proved to be difficult even with drug treatment. Neither is the need to shoot in a private and in a more impersonal setting, like a shooting gallery, easy to change or substitute. On the other hand, lending, borrowing or sharing needles in Puerto Rico might be easier to substitute for the use of new needles, in a society where needles are easily available in drug stores, without need of a prescription. Under these circumstances the need for sharing, lending or borrowing is not so pressing. Furthermore, buying a new needle takes less cognitive planning, time and effort than cleaning needles with bleach; a behavior addicts in Puerto Rico have not shown much enthusiasm to accept as of yet. However, as the Island provides the setting and ways for acquiring new needles, this is a behavior addicts have already started to practice. It seems that for Island IV drug users a more effective message should be to use new needles, because buying new needles is easier than cleaning needles and is much more cheap than getting infected with AIDS.

The high prevalence of HIV among IV drug users in this study should be enough reason for all health and

drug related private and public agencies, as well as policy makers and citizens in general, to begin taking seriously this high risk group for the transmission of AIDS to the community. Massive preventive and treatment programs are urgently needed to arrest the transmission of this deadly disease.

**Resumen:** En este análisis se entrevistaron y analizaron 385 usuarios de drogas intravenosas reclutados en varios vecindarios del área metropolitana de San Juan. Los usuarios de drogas intravenosas (UDI), independientemente de raza, grupo étnico o medio ambiente geográfico, continúan practicando conductas de riesgo para el contagio del virus de inmunodeficiencia humana (VIH). En general, los UDI incluidos en este análisis son jóvenes. Sin embargo, se encontró que los grupos de puertorriqueños e hispanos tenían un nivel de escolaridad menor al de los blancos y negros de los Estados Unidos. El hecho de que casi la mitad de los UDI puertorriqueños residiendo en los Estados Unidos Continentales reportaran actividades ilegales como fuente de ingreso, sorprendió a los investigadores. Tal y como fuera hipotetizado, casi la mitad de los UDI puertorriqueños en la isla informaron vivir con sus padres. Los UDI en la isla de Puerto Rico continúan practicando conductas de riesgo, se inyectan drogas y utilizan los "hospitalillos" con más frecuencia y son menos propensos a desinfectar las agujas y a utilizar condones que los UDI puertorriqueños, blancos y los negros que residen en los Estados Unidos. Los UDI son el grupo de mayor riesgo para el contagio del síndrome de inmunodeficiencia adquirida (SIDA) entre los puertorriqueños que residen en Puerto Rico y en Estados Unidos. Los UDI son también el grupo con mayor riesgo de contagio heterosexual y la mayor fuente de contagio perinatal de la enfermedad. Por lo tanto, los recursos para prevenir el SIDA en Puerto Rico son más necesarios entre los UDI, donde el 44.5% de los sujetos han obtenido resultados positivos en la prueba del VIH.

#### Acknowledgements

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**LA CASA DE TU SEGURIDAD**

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# REVIEW ARTICLE

## Anterior Segment Laser Surgery: Basics

Jorge L. Fernández-Bahamonde, MD\*

An excellent performance at surgery requires a complete knowledge of the anatomy, adequate tools, good judgement for proper case selection, mastering the appropriate techniques, and experience handling potential complications. Knowing the fundamentals of the tools used will determine the success of most of the above; laser surgery is a very good example of this.

A review of the basics aspects of anterior segment laser surgery will be presented, including a discussion of the different laser tissue interactions, the most common laser types and some general clinical rules.

### History

The beginning of this century set the foundation for the development of the L.A.S.E.R. (Light Amplification by Stimulated Emission of Radiation). Concepts like the "photon", the relationship between its energy and the wavelength of light (energy=Planck's constant  $\times$  light velocity/wavelength) and the "spontaneous emission of fluorescence" described by Planck, together with Einstein's "stimulated emission" made possible all the theory behind the laser research of the last 30 years.

Odd enough, clinical applications preceded the technology; attempts to photocoagulate the iris and retina were made in 1916 by Verhoef and Bell focusing the sunlight with a lens, repeated in the 50's by Meyer-Schwickerath, who later reported a patent iridotomy using a xenon arc photocoagulator. The 60's saw the use of the ruby laser in the anterior segment, this decade was followed by the widespread use of the continuous wave argon laser in the late 70's for iridotomies and trabeculoplasties and the clinical application of the Nd:YAG laser a few years later.<sup>(1, 2, 3, 4)</sup>

### Basic physics.

To have a successful laser beam several conditions are necessary. The source, either gas, liquid or solid should

contain atoms with electrons capable of sustaining prolonged excited states (metastable states), those atoms when further excited by either an electric current or a flashlamp will have a greater proportion of their electrons in higher energy levels (population inversion) an unstable situation that leads to the emission of photons to achieve more stable levels. In a high energy state each photon produces two identical photons after hitting another electron (spontaneous emission), the resultant cascade effect forms the basis of the laser beam.<sup>(1, 2)</sup>

A good phase correlation across the beam (spatial coherence), lack of variation with time (temporal coherence), parallel alignment of the "rays" in the beam (collimation), high intensity and monochromaticity are the properties that make laser light different from regular

Table I. Ophthalmic Lasers.

Name	Wavelength (nm)	Source	Use
Argon	488.8 (blue) 514.5 (green)	Argon	Photocoagulation
CO <sub>2</sub>	10600 (infrared)	CO <sub>2</sub>	Photovaporization Photocoagulation
Copper	510 (green)	Copper	Photocoagulation
Vapor	578 (yellow)		
Excimer	126-351 (ultraviolet)	Various	Photoablation
Erbium:	1228	Erbium	Photodisruption
YLF	(infrared)		
Gold	628 (red)	Gold	Photoradiation
Vapor			Photocoagulation
Helium-Neon	633 (red)	Neon	Aiming
Krypton	531 (green) 568.2 (yellow) 647 (red)	Krypton	Photocoagulation
Nd:YAG	532 (green) 650 (red) 1064 & 1300 (infrared)	Neodymium	Photocoagulation Photocoagulation Photodisruption & Photocoagulation
Ruby	694.3 (red)	Cromium	Photodisruption & Photocoagulation

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light. In practice, this occurs in a cavity or "tube" which contains a system of mirrors; a shutter opens when the beam is optimal, delivering energy either as a continuous wave (conventional argon laser or continuous mode Nd:YAG laser) or as a pulse in which the energy is highly packed and released in a very short period of time (pulsed argon laser, Q switch and mode locked Neodymium:YAG lasers). The general characteristics of the ophthalmic lasers are summarized in Table I. (2)

### Effects in Biologic Tissues

Light is either absorbed or scattered by the tissue. At energy levels lower than that produced by the Q-switch or modelocked lasers photons from visible or ultraviolet lasers excite outer electrons of the target tissue to higher energy levels. Excess electron energy in the tissue may be liberated through a chemical reaction (photochemical), an increase rate of vibration (thermal), spontaneous emission, or collision with another atom or molecule. Additionally, infrared lasers transfer energy directly increasing the vibration of the affected molecules (heat energy). High energy lasers like the Q-switch Nd:YAG tear electrons from the tissue producing a "plasma" state (a collection of ions and electrons), the plasma has the mechanical properties of gas and the electrical behavior of metal. Shock and acoustic waves produced by the expansion of plasma lead to tissue disruption. (1, 3)

The laser effects over biologic tissue are divided in three broad categories with five subdivisions, see Table II. At present, the most useful lasers for the ophthalmologist are the photocoagulators and the photodisruptors.

Table II. Laser-tissue effects.

Effect	Characteristics/Clinical Example
I - Photochemical	Exposure longer than one microsec. low energy, usual wavelength below 320 nm.
photoradiation	Irradiation of a choroid melanoma with a Gold Vapor laser after intravenous administration of a hematoporphyrin derivative.
photoablation	Excimer laser corneal incisions, limited damage to surrounding tissue, no coagulation effect.
II - Thermal	Low energy, exposure longer than one microsecond, wavelength above 450 nm. Extent of injury proportional to the magnitude and duration of temperature increase.
photocoagulation	Argon laser trabeculoplasty, cyclodestruction with coagulation mode of Nd:YAG laser.
photovaporization	Carbon dioxide cutting of tissue, accompanied by damage to surrounding tissue, coagulation and cautery.
III - Ionizing	High energy, exposure shorter than $2 \times 10^{-9}$ s. electrons are removed from atoms and molecules.
photodisruption	Neodymium: Yag laser capsulotomy.

### Photocoagulators

The laser wavelength, exposure time, amount of energy delivered per area and pigmentation of the target tissue are the main factors in the denaturation of proteins and nucleic acids, i.e. photocoagulation. Maximal absorption, a quality dependent both on the wavelength of light and the characteristics of the target tissue determines the efficiency for conversion of laser energy into heat to obtain the desired effect. (1, 3)

Melanin is the most common and best absorber of the pigments present in the human eye, with an absorption range between 400-700 nm, it offers several alternatives for laser selection. In the anterior segment the argon green, the argon blue-green and even the krypton red should not be significantly different, however tradition and the production of more superficial and visible burns make the argon blue-green laser the most popular photocoagulator. The argon blue-green is widely used for trabeculoplasties, iridotomies, iridoplasties and coreoplasties. (1, 3)

Hemoglobin absorbs red light poorly, it has a preference for the blue and the green light. Heating the hemoglobin and the collagen cause thrombus formation and shrinkage of the vessel tissue which stop the circulation distal to the affected area. Closure of small blood vessels is easily achieved with the argon laser superficial burn, however larger vessels require a deeper burn, the infrared beam of the Nd:YAG laser in the continuous wave (coagulation mode, exposure time 0.2-0.5 seconds) is very useful for treating large caliber vessels like the esophageal varices. (1)

Usually applied through a slit lamp, the use of a contact lens with anti-reflective coating facilitates the application of the argon laser in the anterior segment. The lens keeps the lids open, improves control over the eye, and reduces laser and light reflections avoiding hazardous consequences to an observer and improving visibility. A contact lens with a magnifier button (like the Abraham's or Wise's lenses for iridotomies) decreases the spot size, provides a sharper focus, a shorter focal length with less potential damage to anterior and posterior structures. The methylcellulose needed for lens coupling absorbs excess heat, which decreases the incidence and severity of corneal burns.

For a given power setting (watts) and exposure time (seconds) the temperature increase will be inversely proportional to the spot size (microns), this concept forms the basis of most iridotomies techniques. Spot size settings are accurate only if the tissue is located at the exact working distance of the slit lamp. Proper focus of the slit lamp using a "fogging" technique is essential to obtain the correct spot size.

### Photodisruptors

Photodisruptors use an special shutter that liberates "bursts" of energy (1-15 mJ) in a very short time (nanoseconds). The less complex and more widely available photodisruptor in the U.S., is the Q-switch Nd:YAG laser, it produces single or multiple pulses "bursts" of  $2-14 \times 10^{-9}$  seconds. Mode locked lasers are more

complex and not very common outside Europe, they deliver a "train" of shorter 7-9 spikes of energy in a  $3 \times 10^{-8}$  pulse interval. A low power Helium-Neon 632.8 nm red laser is incorporated to the delivery system (usually an slit lamp) to focus the invisible 1064 nm laser, the use of a multiple beam for the aiming laser (2 or 3 red spots) makes possible a sharp and reproducible end-point, a requisite for precise surgery.

The tissue effects are identical for both types of Nd:YAG lasers, plasma formation creates shock and acoustic waves that essentially cut through tissue. Initially popularized for posterior capsulotomy, the Nd:YAG is very helpful for laser iridotomy, limited iris bleeding is not uncommon, but usually it stops with mild pressure over the eye. Other less frequent applications in the anterior segment include lysis of vitreous strands trapped into surgical wounds and attempts to re-establish filtration by reopening blocked trabeculectomies.<sup>1, 2, 3</sup>

As in argon laser surgery, proper focus of the slit lamp and use of a contact lens are essential for all anterior segment Nd:YAG laser procedures.

## Hazards

Most ophthalmic lasers are classified as significant hazard to the skin and eyes or unsafe even for momentary viewing without safety equipment (Class IV and Class III b lasers respectively).<sup>2</sup> Obviously the patient is the one at greatest danger, anterior segment procedures create a significant risk to the retina; a precise focus helped by adequate slit lamp settings and the use of a contact lens, plus extreme caution with an strict attention to details should avoid this problem, particular complications resulting from the different treatment alternatives should be evaluated which each type of procedure individually. The surgeon is protected by the filters in the laser slit lamp and the anti-reflective coating of the contact lenses. Paramedical personnel are at risk of eye or skin burns from reflected laser light; the use of protective goggles, instructing them to look away from the laser area, and limiting visits to the laser room to those absolutely necessary should prevent potential complications.

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Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

**Indications:** Yocon<sup>®</sup> is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

**Contraindications:** Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

**Warning:** Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

**Adverse Reactions:** Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.<sup>1,2</sup> Also dizziness, headache, skin flushing reported when used orally.<sup>1,3</sup>

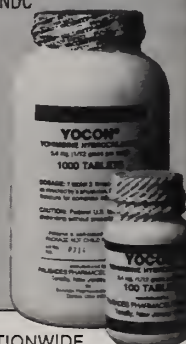
**Dosage and Administration:** Experimental dosage reported in treatment of erectile impotence.<sup>1,3,4</sup> 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.<sup>3</sup>

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# Historia de la Medicina

## Historia de la Fisiatría en Puerto Rico 1940-1973\*

Herman J. Flax, MD, FACP\*\*

La Fisiatría es aquella especialidad de la medicina que ayuda física y mentalmente a las personas incapacitadas a funcionar con su mayor potencial posible en la sociedad. Aunque todas las medidas médicas conocidas pueden ser empleadas en el tratamiento de los incapacitados, por razones de definición se les suele dividir generalmente en las modalidades de Medicina Física y Rehabilitación. La Medicina Física consiste en el uso de los agentes físicos, tales como luz, agua, electricidad, masaje, manipulación y ejercicio para suplementar los más específicos procedimientos médicos y quirúrgicos prescritos por el médico. La Rehabilitación consiste en el restablecimiento del impedido hasta la máxima utilidad física, mental, social, vocacional y económica de la que es capaz. El retorno al empleo, aunque importante, no es el único objetivo válido de la rehabilitación. Además de convertirse en un jornalero, debe enseñarse al impedido a valerse por sí mismo, a vivir independientemente de los cuidados de otras personas.

El concepto fisiátrico de un total cuidado médico fué el primer paso para que el paciente fuera visto y tratado no como un sistema específico o un patrón de enfermedad, sino como un completo ser humano. Esta filosofía del total cuidado médico trajo consigo el desarrollo del trabajo en equipo, usando las habilidades especializadas de médicos y cirujanos, de terapeutas físicos y ocupacionales, de trabajadores sociales, terapeutas del habla y del oído, enfermeras, consejeros vocacionales, terapeutas recreacionales, sicólogos, prototistas y ortotistas, para cubrir las necesidades de los casos más difíciles. Esta idea actualmente ha sido llevada a la siquiatria, cardiología y enfermedades pulmonares crónicas, con el establecimiento de programas en los centros diurnos para los pacientes con deficiencias siquiátricas, cardíacas y respiratorias. Cada una de estas entidades médicas individuales tienen hoy día sus propios "equipos", con la única diferencia de ser un grupo más reducido, para rehabilitar a sus pacientes en el verdadero sentido de la palabra. Poco a poco, durante este último cuarto de siglo, se han ido infiltrando a todas las ramificaciones de los cuidados médicos las enseñanzas de la medicina de rehabilitación y de los fisiatras. Hoy día el paciente es

visto por el especialista como un total ser humano y no como una parte enferma. El cuidado médico no está completo hasta que el paciente haya sido entrenado para vivir y trabajar con lo que le queda. Lo mismo que la ciencia médica está añadiendo años a la vida hoy, así también nosotros debemos añadir vida a los años. En pocas palabras, ésta es la verdadera filosofía de la medicina física y rehabilitación.

### El Licenciado Guillermo Atilés Moreu

Antes del año 1940 y de la segunda guerra mundial, la legislación social de Puerto Rico pagaba por ciertos servicios fisiátricos a través del Gobierno Federal. Existía alguna terapia física y ocupacional en el Departamento de Salud para niños lisiados, y había también un programa de rehabilitación vocacional en el Departamento de Educación, pero sólo de nombre.

La verdadera realización de la fisiatría en Puerto Rico surgió en el 1944, cuando el finado Lcdo. Guillermo Atilés Moreu, entonces administrador del Fondo del Seguro del Estado, escuchó al Doctor Harold D. Storms, director de medicina física del Centro de Rehabilitación de la Junta de Compensación de los trabajadores de Ontario, Canada, en una reunión en Seattle, Washington. Anteriormente a esta época las únicas medidas de rehabilitación para los trabajadores lesionados en Puerto Rico consistían en calor y masajes en el Dispensario de San Juan ofrecidos por un masajista conocido más tarde como quiropráctico, Señor Jesús Amadeo, quien trataba a sus pacientes "espiritual, mental y físicamente". El Lcdo. Atilés estaba tan impresionado con los resultados del método del Doctor Storms que, a su regreso a Puerto Rico, organizó inmediatamente una beca para el entrenamiento de médicos y terapeutas en los Estados Unidos.

El primero de estos médicos fué el Doctor Salvador Arana Soto, quien estudió en la Escuela de Medicina de Northwestern bajo la dirección del Decano de los fisiatras americanos Doctor John Coulter. El Doctor Arana organizó el primer programa de rehabilitación en Puerto Rico en el edificio F. y J. Carreras en la marina de San Juan en el 1946. Su jefe de terapia física fué la señorita Priscilla Jusino, su jefe de terapia ocupacional, la señorita Carmen Pura Pérez, su trabajadora social, la señora Irene Bravo de Bonilla, y su asistente fué un joven inspector médico y cirujano del Fondo del Seguro del Estado, Doctor Herman J. Flax. El doctor Flax estuvo yendo continuamente a los Estados Unidos y el Canada

\* Conferencia dictada ante la Academia Puertorriqueña de la Historia de la Medicina, 13 de marzo, 1973

\*\* Jefe, Servicio de Medicina de Rehabilitación, Facultad Médica, San Juan, VAMC.

para sus estudios bajo el Doctor George Morris Piersol en Philadelphia, el Doctor Storms en Canadá y el recientemente abierto Centro Modelo de Rehabilitación del Doctor Howard A. Rusk en la Ciudad de Nueva York.

El Fondo del Seguro del Estado continuó ampliando su programa de rehabilitación y se trasladó a un local más moderno y espacioso en el Professional Building en la Avenida De Diego en Santurce, en Abril de 1949. Aquí el centro de rehabilitación fué combinado con un programa de cirugía para el tratamiento del trauma. Los obreros gravemente lesionados tuvieron la ventaja de una mejor cirugía, además de inmediatas medidas fisiátricas. Durante este tiempo fué añadido un programa organizado de recreación para los pacientes ambulatorios de la Isla que estaban hospedados en la mansión Georgetti, en la calle Hipódromo en Santurce. El Doctor Arana renunció, y el doctor Flax fué nombrado director de medicina física y rehabilitación con el traslado del centro en el 1949.

Muchos terapeutas y pocos médicos fueron enviados a los Estados Unidos y al Canadá para entrenamiento durante esta época. Dos de los médicos originales fueron el Doctor Aúreo Calderón, que tabajó y fué director de medicina física y rehabilitación en el Fondo del Seguro del Estado hasta su retiro, desde 1950 hasta 1972, y el Doctor Victor Cucurella, un médico refugiado español, ahora muerto, que fué un noble pionero del programa de rehabilitación de Puerto Rico en los años 50.

El Doctor Flax regresó a los Estados Unidos en 1951 para concluir sus estudios, y fué el primer especialista titulado en medicina física y rehabilitación al aprobar los exámenes de la Junta Examinadora Americana en su especialidad en aquel año.

#### **Primer Instituto Sobre Problemas De La Rehabilitación En Puerto Rico.**

Probablemente el acontecimiento más significativo en los comienzos de la medicina física y rehabilitación fue el Primer Instituto sobre Problemas de Rehabilitación llevado a cabo en el auditorio de la Escuela de Medicina Tropical en San Juan el día 4 de febrero de 1950. El Fondo del Seguro del Estado produjo la chispa para la organización de este congreso, secundado por el Departamento de Salud y el de Educación. Invitada como coauspiciadora de esta reunión, estuvo la Sociedad Internacional Para el Bienestar de los Lisiados (llamada actualmente Rehabilitación Internacional), cuya oficina estaba en la Ciudad de Nueva York.

El comité organizador estaba compuesto por el Ldo. Guillermo Atilés Moreu, del Fondo del Seguro del Estado, presidente, la doctora Blanca Trelles de Vázquez, directora de la sección de niños lisiados del Departamento de Salud, y el señor Manuel Hernández, director de la división de rehabilitación vocacional del Departamento de Educación. El doctor Natalio Bayonet, director médico, y el doctor Herman J. Flax, director del servicio de medicina física y rehabilitación, ambos del Fondo del Seguro del Estado, estuvieron también presentes en este comité.

Distinguidos visitantes de los Estados Unidos, todos

los cuales fueron instrumentos en el crecimiento de la medicina física y rehabilitación en Puerto Rico fueron:

1. Doctora Bell Greve, trabajadora social y abogada, secretaria ejecutiva de la Sociedad Internacional Para el Bienestar de los lisiados y directora del Centro de Rehabilitación de Cleveland,
2. Doctor Henry Kessler, cirujano ortopeda, distinguido autor de muchos libros de texto sobre ortopedia y rehabilitación y director del Instituto Kessler de Rehabilitación, de East Orange, en Nueva Jersey,
3. El señor Michael J. Shortly, director de la Agencia Vocacional de Rehabilitación de la Seguridad Federal, en Washington D.C.,
4. El señor K. Vernon Banta, secretario ejecutivo del comité presidencial para empleo nacional de los impedidos físicos de la Agencia de Seguridad Federal, en Washington D.C.,
5. La señorita Mildred Elson, R.P.T., secretaria ejecutiva de la Asociación Americana de Terapia Física, en la Ciudad de Nueva York,
6. La señorita Eva Otto, secretaria del campo educativo en la Asociación Americana de Terapia Ocupacional, en la Ciudad de Nueva York,
7. El señor Holland Hudson, director de los servicios de rehabilitación de la Asociación Nacional de Tuberculosis,
8. La Doctora Romaine P. Mackie, especialista de las escuelas para los físicamente impedidos, en la oficina de educación de la Agencia de la Seguridad Federal, en Washington D.C.,
9. El señor H.B. Cummings, asistente ejecutivo en la oficina de rehabilitación vocacional de la Agencia de Seguridad Federal, en Washington D.C.,
10. El Doctor Donald A. Covalt, director clínico en el Instituto de Medicina Física y Rehabilitación de la Escuela Universitaria de Medicina de Nueva York en la Ciudad de Nueva York, y
11. El señor Eugene J. Taylor, asistente ejecutivo en el Instituto de Medicina Física y Rehabilitación de la Escuela Universitaria de Medicina de Nueva York en la Ciudad de Nueva York.

Las actas de este seminario han sido publicadas, pero no obstante merece la pena hacer un breve sumario, ya que esta reunión allanó realmente el camino debido al tremendo auge que alcanzó esta práctica médica durante la pasada década.

La mañana del primer día, primero de febrero de 1950, estuvo dedicada a la presentación del programa de rehabilitación en Puerto Rico. La doctora Blanca Trelles organizó el primer programa de niños lisiados para el Departamento de Salud de Puerto Rico, en 1939. En esta época, las principales causas de condiciones lisiadas eran: 1. Parálisis infantil, 2. Anomalías congénitas, 3. Fracturas, 4. Osteomielitis, 5. Tuberculosis de los huesos, y 6. Perlesía cerebral.

En 1961 la primera terapeuta física graduada, señorita Augusta V. Stubbe (ahora De Besosa), fué asignada por el Departamento de Salud Pública para desarrollar un programa de terapia física dy rehabilitación en Puerto Rico. El primer taller de abrazaderas en la Isla fué abierto por este programa en 1941. Los servicios fueron dados en los tres hospitales de distrito y en algunas instituciones



privadas. El hospital de distrito fué provisto de los servicios de un cirujano ortopeda, una enfermera ortopeda, un terapeuta físico, un terapeuta ocupacional, una enfermera auxiliar y también de material y equipo ortopédico. El personal técnico servía como base de consulta al hospital también, y el hospital daba a cambio veinte camas para el uso exclusivo de la sección de niños lisiados. Además de cirugía ortopédica, cirugía plástica y servicios oftalmológicos, esta sección trabajó mucho en la salud pública usando enfermeras de salud pública y trabajadores sociales médicos.

Había muchos paciente con resíduos de poliomielitis, y estos casos fueron enviados a la Casa de Convelescentes en Guaynabo (hoy conocida como Hospital de Niños Convalescentes) para el tratamiento de la Hermana Kenney y otras medidas de rehabilitación, además de una enseñanza académica. Este centro trataba a pacientes hasta los veintiún años, y a esta edad eran enviados a la división de rehabilitación vocacional del Departamento de Educación. El doctor Peter Sabatelle fué el primer cirujano ortopeda llamado de los Estados Unidos, y le siguieron muy pronto los doctores Robert Freedman y Leon Sheplan.

Una de las frases que la doctora Trelles de Vázquez pronunció por esta época es igualmente válida 23 años después. Ella dijo: "La invalidez es generalmente causada por desajustes sociales y emocionales más que por incapacidad física".

El doctor Antonio Acosta Velarde pronunció una docta disertación acerca de la "Rehabilitación de los pacientes de tuberculosis en Puerto Rico", pero apenas se hizo nada, a no ser el cuidado sanitario. El doctor Ramón Fernández Marina fué un polemista pacífico cuando puso en discusión la "Rehabilitación del paciente siquiátrico en Puerto Rico". Dijo: "Quiero aclararles la total carencia de facilidades para rehabilitar a los pacientes siquiátricos en Puerto Rico".

El Doctor Fernando Monserrate sometió a discusión la función de la "Universidad de Puerto Rico en la preparación de técnicos para la tarea de la rehabilitación", y se vió forzado a admitir que sólo se había ofrecido entrenamiento en el campo de los trabajadores sociales médicos.

El doctor E. Blas Ferraouiili introdujo la "Rehabilitación de los Veteranos en Puerto Rico". La Administración de Veteranos del Hospital de San Patricio fué abierta el primero de Noviembre de 1946 y fué el primer Hospital en Puerto Rico para proveer un servicio de medicina física y rehabilitación. El servicio de medicina física y rehabilitación estaba bajo la dirección del jefe de la sección de ortopedia, Doctor Peter Sabatelle, e incluía ambas unidades de terapia física y ocupacional. Además había un programa de recreación bajo servicios especiales, un servicio social y un servicio de rehabilitación vocacional y educacional. Este último programa fué establecido el 27 de Junio de 1949 para el reentrenamiento y educación de los veteranos incapacitados en servicio militar. A finales de 1949, 1065 veteranos incapacitados recibieron beneficios de rehabilitación vocacional y 444 estaban en las listas del 1ro. de febrero de 1950.

El Doctor Ferraouiili insistió: "La Administración de

Veteranos de Puerto Rico se esfuerza en conseguir un programa completo de rehabilitación que no sólo ofrecerá al veterano lesionado el mejor cuidado médico y quirúrgico posible, sino que también proveerá de servicios que restaurarán su condición mental y física hasta el máximo grado posible".

El señor Manuel Hernández, director de la oficina de rehabilitación vocacional, declaró que su oficina fué establecida en Puerto Rico en agosto de 1936 y era responsable de la actual administración de los servicios de rehabilitación a hombres y mujeres impedidos cuya condición física y mental los había dejado incapacitados vocacionalmente. En la actualidad, el presente programa de rehabilitación vocacional comenzó en 1943. Esta agencia abrió un taller para la fabricación de miembros artificiales, abrazaderas y calzados ortopédicos bajo la supervisión del primer protetista entrenado y certificado puertorriqueño, señor José Laboy, en marzo de 1948. Otros servicios de rehabilitación incluían programas de reentrenamiento vocacional en el Hospital de Tuberculosis en Cayey, abierto en 1948, un taller industrial para los ciegos en el Instituto para Ciegos Loaíza Cordero, fundado en 1919 como el "Instituto para Niños Ciegos", y un taller para pulir lentes, ambos abiertos en 1948. Durante el año Fiscal de 1949, fueron rehabilitadas un total de 567 personas impedidas, con un costo de 120.112 dólares. Estas personas obtuvieron un promedio de salario semanal de 16 dólares, que suponía un ingreso anual de 471,744 dólares. Esto implicaba una restitución anual que triplicaba el dinero invertido en su rehabilitación.

La "Rehabilitación de los Obreros Lesionados en Puerto Rico" fué sometida a discusión por el Doctor Flax. Por este tiempo el cuerpo de medicina física y rehabilitación del Professional Hospital estaba compuesto por un director médico, especialista en medicina física y rehabilitación, 26 terapeutas físicos y ocupacionales y ayuda clerical. Desde que el centro estuvo unido al hospital por la planta superior, tuvieron fácil acceso los consultores en cada uno de los campos de medicina y cirugía. El Fondo del Seguro del Estado había montado un programa práctico que se asemejaba mucho a los centros de rehabilitación ya existentes en Ontario, Canadá, para los obreros impedidos. Por primera vez en Puerto Rico se produjo una acción recíproca entre el médico, el terapeuta, el trabajador social, el protetista y el consejero vocacional.

Los días siguientes estuvieron dedicados a escuchar a un grupo de expertos de los Estados Unidos y a la presentación de pacientes por cada agencia. Finalmente, la asamblea se dividió en grupos individuales para discutir y presentar resoluciones. Estas propuestas, presentadas por la asamblea y recopiladas en el libro, "Actas del Primer Instituto sobre Problemas de Rehabilitación en Puerto Rico", constituyó realmente el trabajo de base para las futuras prácticas fisiátricas en Puerto Rico.

En marzo de 1950, la Sociedad Nacional de Niños y Adultos Lisiados, Capítulo de Puerto Rico, fué organizada cuando el Lcdo. Guillermo Atilés Moreu y el Doctor Herman J. Flax se reunieron con los representantes de esta organización en Washington. La Primera

Venta de Sellos de Pascua Florida fué inaugurada unas semanas más tarde con sellos traídos de Washington.

En 1950, la Universidad de Puerto Rico inauguró la actual Escuela de Medicina en el Edificio de la Escuela de Medicina Tropical. El discurso-demostración de electroterapia fué presentado a los alumnos de la primera clase de fisiología en 1951, y en su tercer año, en 1953 este mismo grupo de alumnos recibió ocho horas de discursos formales sobre medicina física y rehabilitación a cargo del doctor Flax, que estaba nombrado profesor asistente clínico de medicina física y rehabilitación en el Departamento de Cirugía dirigido por el doctor José Noya Benítez.

En enero de 1953, el Fondo del Seguro del Estado abrió una escuela de terapia física y ocupacional bajo la dirección del doctor Harold D. Storms, que había venido a Puerto Rico a encargarse del centro de rehabilitación de esta agencia en 1951. Esta escuela era la única que graduaba estudiantes expertos en ambas terapias, física y ocupacional. En 1954, fué acreditada por la Asociación Médica Americana, la Asociación Americana de Terapia Física y la Asociación Americana de Terapia Ocupacional. La escuela fué afiliada al departamento de Medicina Preventiva y Salud Pública de la Escuela de Medicina de la Universidad de Puerto Rico en 1956, y en 1961, la Universidad otorgó los primeros grados de Bachillerato de Ciencia en Terapia Física y Ocupacional. El doctor Eugene H. Weissenberg fué nombrado director de esta escuela, y también jefe de medicina física y rehabilitación del Centro de Rehabilitación del Fondo del Seguro del Estado a la muerte del doctor Storms en el 1955. La señora Lutgarda Vega de Piñero fué la primera directora técnica del currículo de terapia física y el señor Esteban López el primer director técnico de terapia ocupacional y coordinador de ambas escuelas, puestos que ambos desempeñan hoy día.

El Capítulo Puertorriqueño de la Asociación Americana de Terapia Física fué organizado en 1947, y la señora Nadine Rivera fué su primer presidente. La legislación para controlar la práctica de terapia física en Puerto Rico fué aprobada por la legislatura en 1962, como lo manifiesta la ley número 114, y fué inmediatamente firmada por el Gobernador Luis Muñoz Marín. Por esta época, y como lo exigía ésta nueva ley, se estableció una junta examinadora en Puerto Rico con el fin de examinar y licenciar a los terapeutas físicos que fueran a ejercer en Puerto Rico. El Doctor Carlos T. Armstrong Ressay fué el primer presidente de esta junta y estuvo asistido hábilmente por las señoras Consuelo Benz de Núñez y Carmen Collazo de Schweitzer, las cuales habían trabajado afanosamente en pro de la rehabilitación de esta ley.

El Capítulo Puertorriqueño de la Asociación Americana de Terapia Ocupacional fué fundado en 1950, y su primer presidente fué el señor Esteban López Fernández. La Terapia Ocupacional se convirtió en una especialidad con licencia en Puerto Rico en 1968, cuando el Gobernador Roberto Sánchez Vilella firmó el Proyecto de Ley número 137, enmendado en 1970 por el Proyecto de Ley número 89. El primer jefe de la junta examinadora de Puerto Rico fué la señora Luisa M. Lugo, y los demás miembros fueron: señorita Haydeé Acevedo, señorita

María P. Christian, señorita Zaida Berríos y señora Dominga Vázquez.

En septiembre de 1950 la Universidad de Puerto Rico aprobó el establecimiento de unos estudios postgraduados para consejeros vocacionales, designados sobre todo para orientar a los estudiantes de las escuelas secundaria e inmediata. Este programa suplía en cierto modo a los consejeros vocacionales para adultos impedidos.

En la primavera de 1957 los planes habían cristalizado y comenzaban a enseñarse unos cursos vocacionales en la Escuela de Estudios Sociales de la Universidad de Puerto Rico durante el año académico de 1957-1958.

El primer centro privado de rehabilitación fué inaugurado en 1954 por el Capítulo Puertorriqueño de la Sociedad Nacional de Niños y Adultos Lisiados en el número 51 de la calle Caribe en el Condado, bajo la dirección de la señora María Isabel López de Atilés Moreu. Este centro tenía un director médico, dos cirujanos ortopedas, dos terapeutas físicos, un terapeuta ocupacional, un trabajador social y consultores en todos los campos de la medicina. Además de esto, por primera vez en Puerto Rico, se establecieron en un centro de rehabilitación de pacientes ambulatorios salones para impartir enseñanza de los primeros grados a los niños inválidos, reconocidos por el Departamento de Educación. Este fué un paso importantísimo en el total cuidado del niño excepcional, ya que ello le garantizaba una continuación del cuidado de rehabilitación médica durante todo el año escolar, que a su vez concurría con su formación escolar. En 1962, este centro se mudó a un espacioso lugar de su bello edificio en la calle Ponce en la urbanización Pérez Moris, gracias a la contribución del pueblo de Puerto Rico y especialmente a la Fundación Ferré. En el presente hay una escuela de enseñanza primaria completamente reconocida en el centro, y tres de los cuatro años de escuela superior.

La Casa de Salud para Niños Rosario Bellber fué fundada en Aibonito en 1944 para el cuidado de niños tuberculosos convalecientes. En 1950, bajo la presidencia de la señorita Beatriz Lasalle, esta casa fué organizada para acoger a 50 niños con todo tipo de enfermedades no contagiosas, y para aquellos que habían tenido contacto con la tuberculosis y no podían ser atendidos en sus propias casas.

La Sociedad para la Prevención de la Tuberculosis en los Niños fué organizada el 6 de abril de 1924, mediante los esfuerzos del doctor José Rodríguez Pastor. El 30 de enero de 1929, el Hospital Instituto de Ortopedia y Tuberculosis Osea fué inaugurado en la carretera de Guaynabo, kilómetro 5 1/2. Este hospital estaba provisto de servicio médico y dental, terapia física, terapia ocupacional, enseñanza primaria, recreación y orientación vocacional y un trabajador social.

El Instituto Sicopedagógico de Puerto Rico fue establecido en el 1949 gracias al esfuerzo de la señora María Elisa Gómez de Tolosa. En 1956 este instituto abrió sus locales actuales en la carretera de Bayamón, kilómetro 8 1/2, para el cuidado y entrenamiento especial de los niños mentalmente incapacitados. La señora María M. Martí fué la primera directora. El equipo de tabajadores estaba compuesto por el director, administrador, seis maestros especializados en educar a niños mentalmente retarda-



dos, de los cuales dos eran instructores vocacionales, una terapeuta ocupacional, una enfermera graduada, dos enfermeras prácticas, un masajista y además un pediatra, un siquiatra, un sicólogo, un trabajador social y una dietista.

La Escuela San Gabriel para Niños Sordomudos comenzó en 1902 a cargo de las hermanas del Sagrado Corazón. Esta escuela está reconocida por el Departamento de Educación y es ayudada por la oficina de rehabilitación vocacional. Hay una organización afiliada, el Club de Sordomudos Adultos de San Gabriel, que continúa los intereses escolares en sus graduados.

La Sociedad de Ayuda a los Niños con Parálisis Cerebral fué establecida en 1953, y la primera campaña para recaudar fondos fué en 1954. Esta sociedad coopera con la clínica de parálisis cerebral del Departamento de Salud fundado en 1952 por el doctor Manuel Espinosa. Esta clínica está afiliada con el Fondo Unido de Parálisis Cerebral de los Estados Unidos.

La Casa Deborah para Rehabilitación de Niños Abandonados fué fundada en 1924 por la señora Dorothy Felix y su hija, señorita Helen Felix. En 1940 se abrió una casa en Hato Rey, que más tarde fué vendida, y la casa actual fué fundada en San Martín. Esta casa cobija a unos 30 niños.

El Capítulo Puertorriqueño de la Asociación Nacional de Tuberculosis fué organizado en 1931 bajo la presidencia del doctor José Rodríguez Pastor. Sin embargo, mucho antes, en el 1904 se inició la Liga Antituberculosa de Puerto Rico. Esta organización levantó el primer sanatorio para el tratamiento de niños con tuberculosis, con 30 camas, en el Seboruco del Barrio Obrero de Santurce. En el 1931, en la fusión de las asociaciones antituberculosas, la Liga cambió su nombre a la "Sociedad Antituberculosa de la Capital", bajo la presidencia del doctor Jacobo Simonet. Mediante la venta de Sellos de Navidad, estas asociaciones ofrecen consulta médica y han colaborado en el establecimiento de servicios de rehabilitación en los diversos hospitales y oficinas dedicadas a la erradicación y tratamiento de la tuberculosis.

### **Segundo Instituto Sobre Problemas De La Rehabilitación En Puerto Rico**

El estímulo importante más cercano para la práctica de la medicina física y rehabilitación en Puerto Rico ha sido el Segundo Instituto sobre Problemas de Rehabilitación en Puerto Rico, celebrado en el hotel Caribe Hilton en San Juan del dos al cinco de mayo de 1956. 19 agencias locales auspiciaban y colaboraban. El comité de la organización estuvo compuesto por los diversos subcomités nombrados a la vez que el Primer Instituto, en 1950, bajo la presidencia del Lcdo. Guillermo Atilés Moreu. El comité ejecutivo estuvo presidido por el doctor Harold Hinman, decano de la Escuela de Medicina de la Universidad de Puerto Rico, y el comité del programa por el doctor Reinaldo A. Ferrer, secretario asistente de salud. El doctor Julio B. Ortiz presidió el comité de relaciones públicas, y el señor René Jimenez Malaret el comité de publicaciones. Además, once conferenciantes de los Estados Unidos y 73 expertos locales presentaron trabajos. Esta reunión mostró el enorme desarrollo en la

práctica de medicina física y rehabilitación y las facilidades aportadas en Puerto Rico en seis años cortos pero que señalaron las necesidades todavía no cubiertas. Había aún un retraso en la preparación de personal y en la provisión de facilidades físicas, pero había una necesidad aún mayor de educar a la comunidad sobre los aspectos sociales de la rehabilitación.

Las actas de esta reunión fueron publicadas por el Fondo del Seguro del Estado en 1957.

Poco tiempo después de este Segundo Instituto, el Hospital de Veteranos de San Patricio estableció la primera Residencia Médica aprobada, de un año, en medicina física y rehabilitación en mi servicio, gracias a los esfuerzos del director del centro, doctor Jaime Serra de Chavarry y del jefe de servicios profesionales, doctor José Chaves Estrada. El primer residente fué el doctor Florencio Sáez, que finalizó su residencia en la Universidad de Pensilvania en 1959. Aquel año, el Hospital de Veteranos recibió la aprobación total para un programa completo de Residencia de tres años. El doctor Benigno Fernández y la doctora Mercedes Stefani fueron los dos primeros médicos que completaron su entrenamiento formal en Puerto Rico en 1960 y 1961. Durante los pasados 15 años, 16 fisiatras han recibido todo su entrenamiento completo, y 15 de ellos han permanecido en Puerto Rico. Además, este servicio ha dado entrenamiento a seis médicos de Venezuela y a uno de Colombia. En la actualidad hay cinco médicos puertorriqueños y tres venezolanos recibiendo su entrenamiento como residentes.

El 24 de noviembre de 1969 el Hospital de Veteranos se trasladó a su nuevo hospital de 720 camas en el Campus del Recinto Médico de la Universidad de Puerto Rico. Este hospital cuenta con el más completo programa de rehabilitación en Puerto Rico, incluyendo terapia física, ocupacional y recreacional, un taller de prótesis y ortosis, un departamento de logopedia y audiología, servicios de rehabilitación vocacional incluyendo la educación familiar, consejeros vocacionales, adiestramiento vocacional, pruebas y orientaciones psicológicas, trabajadores sociales asignados exclusivamente para el servicio de medicina de rehabilitación, un gimnasio y una gran piscina de agua con temperatura controlada y bajo techo para ejercicios terapéuticos, además de consulta y tratamiento en todas las especialidades medico-quirúrgicas conocidas.

### **El Campus Del Recinto Médico De La Universidad De Puerto Rico**

La Fisiatría en la Escuela de Medicina de la Universidad de Puerto Rico ha ido progresando firmemente en los últimos quince años gracias a los donativos para demostraciones y adiestramiento proporcionadas por el Gobierno Federal. En 1958, el doctor Robert R. King Jr. fué nombrado director del programa para administrar los fondos Federales. El doctor Eugene J. Weissenberg, que era director de medicina física y rehabilitación del Fondo del Seguro del Estado y director de la Escuela de Terapia Física y Ocupacional, fué nombrado profesor clínico de medicina física y rehabilitación fué establecida bajo el Departamento de Cirugía el 18 de febrero de 1960,



y el doctor King fue ascendido a profesor y jefe de la sección. Al renunciar el doctor King, el doctor Carlos T. Armstrong Ressay asumió en diciembre de 1962 la dirección de la sección de medicina física y rehabilitación, del Hospital Universitario, y de la Escuela de Terapia Física y Terapia Ocupacional, la cual se había convertido en una parte del Campus del Recinto Médico de la Universidad de Puerto Rico. Durante los años siguientes, se añadieron espacio y equipo, y el servicio se convirtió en una parte integral de los programas de enseñanzas y tratamientos del Hospital Universitario.

Se debe mencionar que en julio de 1964 un miembro de esta facultad, el doctor Rafael Berríos Martínez estableció un programa de medicina física y rehabilitación en las Islas Vírgenes.

A la sección de medicina física y rehabilitación se le concedió status departamental en el escalafón de la organización del hospital universitario en el 1966, y se estableció una Residencia de Medicina Física y Rehabilitación en el Hospital Universitario el nueve de marzo del 1967. Durante el año escolar, 1967-1968, la medicina de rehabilitación fué asignada como un estudio electivo durante el internado rotativo. Se añadió al currículo médico en 1969 un nuevo curso con crédito propio, llamado "Cirugía 339, Estudios de Verano", para los estudiantes de cuarto año de medicina, aunque desde 1960 un grupo selecto de estudiantes de verano venía recibiendo ayuda para sus estudios de verano de medicina física y rehabilitación sin crédito.

El Departamento de Medicina de Rehabilitación del Hospital Universitario coordina con otras unidades del Campus del Recinto de Ciencias Médicas. Estas son: El Centro de Rehabilitación de la Oficina de Rehabilitación Vocacional del Departamento de Servicios Sociales del Estado Libre Asociado, el Hospital Industrial del Fondo del Seguro del Estado, el Hospital Municipal de San Juan, el Hospital de la Administración de Veteranos, así como el Hospital Municipal y Subregional de Guaynabo y el Hospital Alejandro Ruiz Soler de Enfermedades del Pecho en Bayamón. El Hospital de Guaynabo es especialmente interesante por sus programas de Apoplejía, en donde se da entrenamiento a un equipo de asistentes de enfermería y de terapia física y ocupacional para que continúen tratando a estos pacientes en sus propias casas después de una corta hospitalización.

Posiblemente el aspecto más singular del Centro de Rehabilitación del Departamento de Servicios Sociales, abierto en 1955, sea la unidad de exploración prevocacional, que usa el sistema Tower y un número de talleres de reentrenamiento vocacional para adultos lisiados situados en el mismo edificio. Mientras el paciente está recibiendo su tratamiento médico y físico, él o ella entran también en un programa de reentrenamiento, como por ejemplo reparar relojes, hacer vestidos, hacer prótesis, abrazaderas y otros trabajos. Hay además 40 camas para hospitalizar a los pacientes gravemente incapacitados, como lo son los parapléjicos y los amputados, y de este modo ellos pueden recibir los beneficios completos del tratamiento de medicina de rehabilitación y además beneficios vocacionales. El 3er. Centro comenzó en 1961 a cargo del señor Domingo Collazo, director de los servicios de rehabilitación vocacional en Puerto

Rico. El doctor Máximo Levin fué y es todavía director médico, y los doctores Ramón Santín y Rafael Berríos Martínez los primeros fisiatras. Este es un centro extremadamente importante para la rehabilitación de personas gravemente impedidas, y afortunadamente está llevando a cabo en la actualidad un extensiva renovación de la planta física con el propósito de dar cuidados a 100 pacientes que están en cama, y eventualmente llegará a ser el centro en el que se dé entrenamiento y tratamiento a los pacientes ambulatorios de los diversos hospitales que hay en el Campus del Recinto de Ciencias Médicas y que venían necesitando de estos servicios especializados.

El Hospital Industrial del Fondo del Seguro del Estado fué inaugurado en 1967. El doctor Ramón Isaías fué su primer director médico, y el doctor Eugene J. Weissenberg su primer jefe del servicio de medicina física y rehabilitación. Este centro para tratamiento de obreros lesionados atiende 200 camas y es un magnífico centro de rehabilitación con servicios completos de terapia física, ocupacional y recreativa, además de servicios sociales y consejeros vocacionales.

El Hospital Municipal de San Juan se trasladó al Campus del Recinto de Ciencias Médicas en 1966, y el doctor Carlos Hidalgo fué nombrado jefe del servicio de medicina física y rehabilitación en 1969. La escuela más importante de enfermería está también situada en esta área, y en ella reciben enseñanza sobre rehabilitación todos los estudiantes de enfermería. La Escuela de Logopedia y Audiología se abrió en 1969 con una ayuda Federal y está bajo la supervisión de la doctora Cruz Cancel. También está bajo construcción en esta misma área el nuevo Hospital Pediátrico, programado para ser inaugurado a finales de este año. La Unidad de Niños Lisiados del Departamento de Salud, situada actualmente en el edificio Tartak en la parada 20 en Santurce será trasladada a unos locales espaciosos en este mismo lugar y será de utilidad como un importante segmento para entrenamiento de todo el personal de rehabilitación. Durante muchos años, este importante programa fué dirigido por la doctora Alma Cajigas, y el doctor Manuel Espinosa, eminente ortopeda, estuvo a cargo de la unidad de parálisis cerebral.

En muy poco tiempo, Puerto Rico ha llegado a ser reconocido internacionalmente por sus dinámicos programas de rehabilitación. Al margen de las invitaciones hechas por Haití, Venezuela, Méjico, Guatemala y Santo Domingo, cuyo propósito era recibir orientación en esta especialidad, se han celebrado en Puerto Rico dos reuniones médicas importantes. La primera fué la Cuarta Conferencia Interamericana sobre Rehabilitación, que se celebró en San Juan los días 20 al 23 de mayo de 1959. Veinte naciones, la mayor parte de Latinoamérica, enviaron delegados capacitados para observar de cerca nuestro trabajo de mejor calidad y llevar nuestro mensaje de vuelta con ellos a sus respectivos países. La segunda fué el Primer Congreso del Caribe sobre Medicina Física y Rehabilitación, celebrado en San Juan los días 25 de abril al seis de mayo de 1966. Asistieron 387 congresistas de veinte países del hemisferio occidental, 186 de los cuales eran médicos, 40 de ellos latinoamericanos.

Más recientemente, en noviembre de 1971, el Congreso Americano sobre Medicina de Rehabilitación celebró su



reunión anual en Puerto Rico bajo la presidencia nacional del doctor Herman J. Flax. Se registraron más de 1400 personas en esta reunión, de las cuales 861 eran miembros de esta organización, la más grande del mundo en este género.

La Asociación Médica de Puerto Rico ha jugado un importante papel en el fortalecimiento de la práctica local de la fisiatría. La Sección de Medicina Física y Rehabilitación fué organizada en 1962 durante la visita de un eminente historiador estadounidense de medicina física y rehabilitación, doctor Sidney Licht. (Menciono al doctor Licht por que el doctor Arana Soto y yo somos viejos amigos suyos y ambos colaboramos con él en numerosas ocasiones, cuando él era editor de una de las primeras revistas americanas sobre esta especialidad, "Occupational Therapy and Rehabilitation", que ahora se llama "American Journal of Physical Medicine"). Ambos, el doctor Arana y yo, somos miembros fundadores de este grupo, que comenzó con once miembros. Desde su fundación, la sección se ha hecho eco de divesos programas científicos notables en Puerto Rico. Entre los más destacados están: "El Primer Congreso del Caribe sobre Medicina Física y Rehabilitación", ya mencionado, "Electrodiagnosis y Enfermedades Neuromusculares", con el doctor Philippe Bauwens, del 17 al 21 de abril de 1967, y "Dolores musculoesqueletales", con el doctor René Cailliet, del 10 al 14 de marzo de 1969. La semana del 19 al 24 de marzo de 1973, el doctor Frederick J. Kottke presentó un curso sobre "Fisiología neuromuscular y tratamiento de las enfermedades de la neurona motora superior". La sección ha participado también activamente en las reuniones regionales de todos los años y en las reuniones anuales también de la Asociación Médica de Puerto Rico. Además, en las reuniones que se celebran cada dos meses, los médicos de otras especialidades de la medicina están invitados a hablar ante los miembros, para establecer más "rapport" entre todos.

No es necesario decir que hay muchos otros grupos filantrópicos públicos y privados, afiliados a las sociedades nacionales, que han jugado una parte en la promoción de la fisiatría en Puerto Rico. Una de las más antiguas y quizás mejor conocidas es la Asociación Puertorriqueña Contra la Parálisis Infantil, que ha ofrecido un programa privado de terapia física desde el año 1949 en el Professional Building. Uno de los grupos más recientes, La Asociación de Distrofia Muscular, Capítulo de Puerto Rico, auspicia una clínica semanal en el Hospital Universitario para niños y adultos con enfermedades neuromusculares. Otras muchas, aunque no poseen programas de rehabilitación, como es conocido, tienen programas de diagnosis y proporcionan equipo y medicamentos para sus clientes. Estas enfermedades tratan todo tipo de males de la medicina, siendo las más recientes adiciones el alcoholismo y la adicción a drogas. Otras, como la epilepsia, enfermedades cardíacas, reumatismo y ceguera, son también demasiado conocidas para que hablemos ahora de ellas.

Se deben mencionar también los clubs cívicos, ya que éstos supuestamente son organizaciones altruistas y no sociales. El "Club de Leones" ha tenido un papel importante ayudando a los ciegos de nuestra sociedad, y el "Club Rotario" fué fundado en Ohio hace unos 50 años, expresamente para atender a los niños lisiados. Todas estas agencias privadas, filantrópicas, desarrollan una importante función en cuanto a la rehabilitación. Mediante sus llamamientos anuales pidiendo fondos, educan al pueblo dentro de sus aparentemente interminables y abrumadoras necesidades en pro de la rehabilitación de nuestra comunidad.

Este es, en breves palabras, en una síntesis brevísima, el origen de la fisiatría en Puerto Rico. Esto es historia muy moderna, que ha comenzado y sucedido en la vida real de todos los miembros de la Academia. Esto sí es una filosofía que ha avanzado al mismo ritmo astronómico del siglo XX. La segunda mitad de este siglo ha venido acompañada del descubrimiento de las milagrosas drogas de la década de los Cuarenta, y esta revolución química ha salvado a millares de vidas de la enfermedad. Aún no hay ningún milagro divino que pueda reponer los cuerpos rotos, las mentes enturbiadas, o frenar la desintegración de la vida misma. Pero aunque se ha logrado mucho en esta bella isla y la práctica de la medicina física y rehabilitación en Puerto Rico está al mismo nivel del resto del mundo, aún se puede y se debe hacer mucho, muchísimo más. Afortunadamente, una vez trillado el camino, es más fácil encontrar la senda.

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# Case Presentación

## Budd Chiari syndrome in a post partum female with adrenal cortical carcinoma. Case report and review of the literature

Carmen González Keelan, M.D.\*  
Carmen Gurrea, M.D.\*  
Ivelisse Ramirez, M.D.+

**Abstract** We report the case of a post partum female whose first manifestation of her adrenocortical carcinoma was an acute Budd Chiari syndrome. We also review previously reported cases of adrenocortical carcinomas with associated Budd Chiari syndrome.

The association of Budd Chiari syndrome to adrenal cortical carcinoma has been rarely reported in the medical literature <sup>1,2,3,4,5,6,7</sup>. The occurrence of the Budd Chiari syndrome during pregnancy and post partum period is also a rare event <sup>8,9</sup>. We present the unique case of a post partum female with adrenal cortical carcinoma who developed an acute Budd Chiari syndrome as the first symptom of an adrenocortical carcinoma, with a rapid, fatal outcome.

### Case Report

A 31 year old female patient G5P3A2 without previous history of systemic illness who had an uncomplicated vaginal delivery 21 days prior to developing right upper quadrant pain and progressive swelling of the abdomen. The patient described good state of health except for occasional low back pain for which she took Motrin, 3-4 tabs daily.

One week prior to admission patient developed fever, nausea, diaphoresis, dizziness and generalized arthralgia. She was prescribed acetaminophen at the local health center and sent home with a diagnosis of a viral syndrome.

The patient denied jaundice, past episodes of yellow tinged sclerae, or skin. She admitted voiding dark colored urine in the days prior to admission, denying cola-like urine. There was no history of acholia, hepatitis or liver disease. There is no family history of liver disease. The

patient denies intravenous drug abuse, alcohol abuse or history of blood transfusions.

The patient had an elective abortion and her fourth pregnancy ended in abortion due to placenta previa. There was no history of preclampsia.

Upon physical examination the patient had prominent collateral circulation, a globose abdomen, and an ascitic wave with shifting dullness. The liver was palpable 10 to 12 cm. below the right costal margin at the right midclavicular line, serum blood glucose of 20 mg. hepatitis Bs antigen non reactive.

She had two episodes of hypotension with poor response to fluid challenge and intravenous dopamine. Twenty hours after admission the patient developed cardiorespiratory arrest unresponsive to resuscitative measures and died.

### Pathology

Autopsy revealed an adrenal carcinoma (see figures 1 & 2) weighing 650 gm. with tumoral thrombosis to the right suprarenal vein extending to the inferior vena cava and obstructing the outflow of the right hepatic vein.

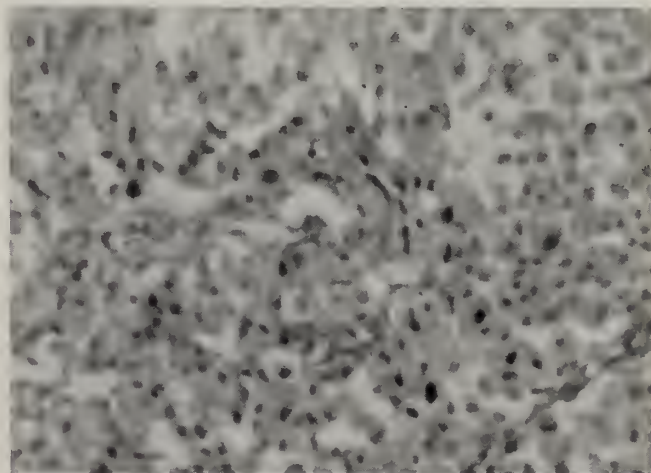


Figure 1: Low power view of adrenocortical carcinoma; nests of cells separated by well vascularized fibrous septae.

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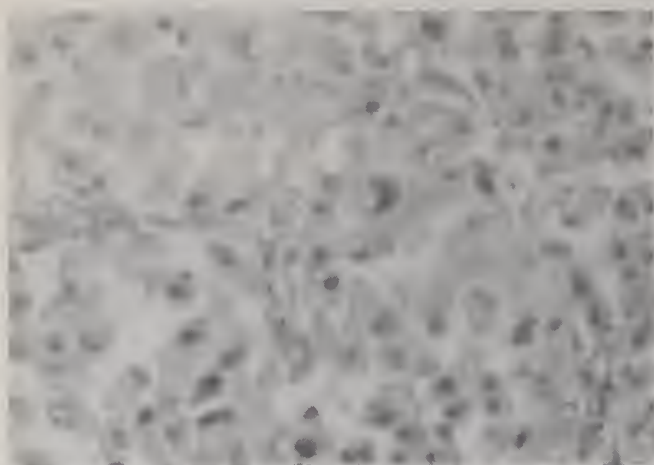


Figure 2: High power view of adrenocortical carcinoma. Dense eosinophilic prominent cytoplasm, binucleation and nuclear pleomorphism as well as necrosis.

Main pulmonary artery embolism was the immediate cause of death in this patient, who developed congestive infarction of the right hepatic lobe with atrophy, ascites of two liters as well as metastatic adrenal carcinoma to lungs.

### Discussion

The Budd Chiari syndrome is caused by obstruction of the hepatic outflow, either at the level of the hepatic veins and or at the level of the inferior vena cava. This syndrome has been observed in patients predisposed to thrombosis by underlying conditions such as paroxysmal nocturnal hemoglobinuria and polycythemia rubra vera, malignancy, as well as during or after pregnancy<sup>10, 11</sup>. Other known causes of the Budd Chiari syndrome include hepatic abscess, or cyst, radiation obliteration of the hepatic veins, and fibrous web across the upper vena cava or just above the left middle hepatic veins.

Few cases of association of the Budd Chiari syndrome to adrenal cortical adenocarcinoma have been previously reported in the medical literature (Table I). We add another case, which has the peculiarity that the patient had another predisposing condition, the post partum period.

Six of the eight reported cases have occurred in females; five of them, in patients between the age of 25 to 32 years. Two of the patients had masculinizing symptoms manifested by hirsutism and other signs. If we compare these findings to the general population with adrenocortical carcinoma, this tumor has been diagnosed more often in females when it secretes hormones: 88 out of 103 occur in females; while only 29 out of 81 nonsecretor adrenocortical carcinomas have occurred in females<sup>12</sup>.

The outcome of patients with adrenal cortical carcinoma who develop the chronic Budd Chiari syndrome is poor, all of them having died within ten months of the onset of symptoms (Table I). Two of the five patients developed virilizing symptoms; one of them resuming menstruation after surgery and showing increased tumoral levels of 17-ketosteroids and 17-deoxy-17-cetogenes explaining these virilizing symptoms.

Table I

### Budd Chiari syndrome in patients with adrenocortical carcinoma

Author	Age	Sex	History	Outcome
Maggi	52	m	S/P surgery	Death two mo. after onset of hepatic symptoms
Dupuy	53	f	6 months menopause	Death 10 mo. after onset of hepatic symptoms
Soscia	25	f	RUQ pain fatigue fever ascites	Death one mo. after exploratory laparotomy due to hepatic vein thrombosis
Copinschi	32	f	amenorrhea hirsutism clitoris hyperplasia	Resumed menstruation after surgery for right adrenal tumor, dying 3 mo. after operation
Michael	30	f	amenorrhea for 12 mo. hirsutism acne	Death on 5th post op day for adrenal carcinoma
Kelsey Carbonnel	unknown 28	f	abdominal distension right lumbar pain, edema	Death 2 days after surgery of adrenocortical carcinoma
Gonzalez	31	f	14 days post partum	Death 7 days after onset of symptoms

Adrenal carcinoma is a rare neoplasm being responsible for 0.2% of all cancer deaths<sup>4</sup>. Nonfunctioning adrenal cortical carcinoma presents most frequently with localizing pain and an abdominal mass and occurring more often in males than in females<sup>12</sup>. Kidney displacement on intravenous or retrograde pyelography will suggest the diagnosis<sup>4, 12, 13</sup>. Hypoglycemia has been associated to adrenocortical carcinoma<sup>12</sup>. The only curative treatment is in block excision. Definite cure cannot be expected from surgery alone. Few patients survive more than 5 years; in fact, half of the patients die within the first two years after diagnosis<sup>12</sup>. Only one case of adrenocortical adenocarcinoma presenting previously to ours<sup>1</sup> and the patient died two days after surgical excision of both the tumor, an eustachian valve thrombus and a clot localized at the right hepatic vein. The autopsy revealed massive microembolisms to the lungs.

Even though conclusions can certainly not be drawn from such a small number of cases, association of the Budd Chiari syndrome to adrenocortical carcinoma seems to be due to the advanced stage of the nonsecretor and, thus, silent neoplasm, particularly in the two cases when it has appeared acutely.

The association of pregnancy and the post partum period with the Budd Chiari syndrome has also been recognized as a rare event the medical literature<sup>8, 10, 11, 14</sup>. The clinical clue to the diagnosis was sudden onset of



abdominal pain and ascites following childbirth. Prognosis is poor, many patients dying within one year from the onset of their illness.

Various treatment schedules including anticoagulant therapies, Rhodiaseit ascitic fluid reinfusion and porto-systemic shunt surgery were not of benefit in the survival of the pregnant or post partum patients.

### Conclusion

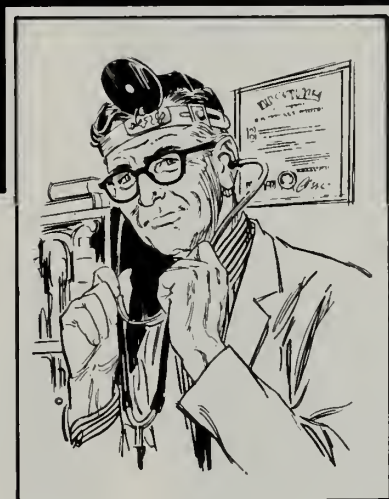
An acute Budd Chiari syndrome occurring in a post-partum female with adrenal cortical carcinoma has been presented. Each of these entities, when associated to the Budd Chiari syndrome has a poor prognosis. Clinical clues to the diagnosis were sudden onset of ascites accompanied by right lower quadrant pain. The possibility of an underlying unsuspected additional predisposing condition to the development of the Budd Chiari syndrome should be thought of; although it is certainly a most rare event. Budd Chiari has been reported more often in non secretor adrenocortical carcinomas in young female patients, probably being an ominous sign of the already extensive disease of this silent carcinoma.

**Resumen** Reportamos el caso de una paciente post parto cuya primera manifestación de su carcinoma de corteza adrenal fue un síndrome agudo de Budd Chiari. También revisamos los casos previamente reportados en la literatura médica en que se ha asociado el síndrome de Budd Chiari al carcinoma de corteza adrenal.

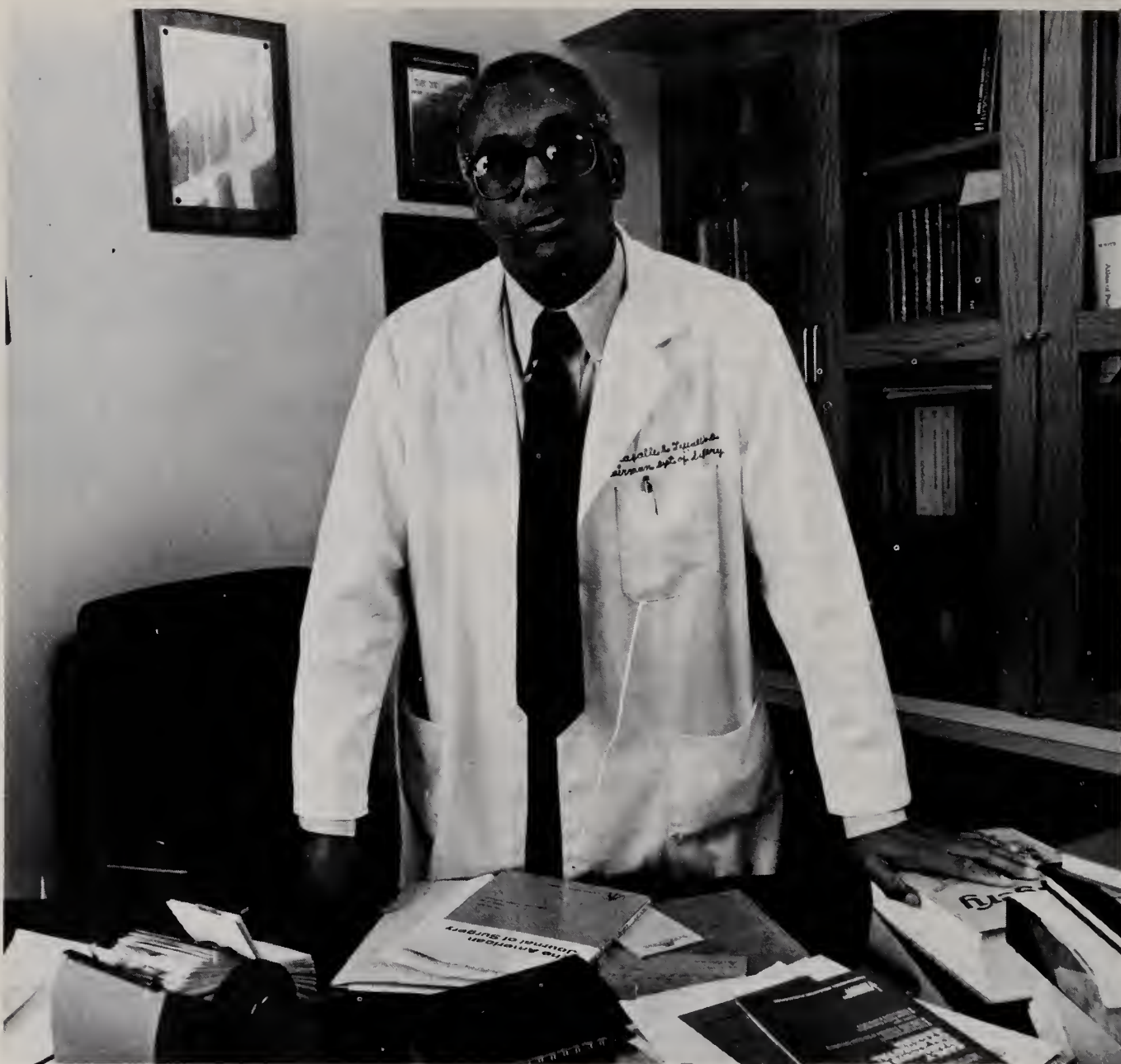
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# Acute Abdominal Manifestations In Patients With Ventriculo-Peritoneal Shunts

Luis A. Ramos, MD\*  
Nathan Rifkinson, MD\*\*

**Abstract:** Five patients with acute abdominal manifestations after revision of ventriculo-peritoneal shunt were identified. Abdominal pain, nausea, vomiting and distention prompted surgical intervention. Clinical evidence of increased intracranial pressure or shunt malfunction were not prominent findings. Exteriorization of the distal (peritoneal) catheter resolved the acute abdominal findings promptly.

Ventriculo-peritoneal shunt has become the treatment of choice for several neurological conditions. Along with its low morbidity and mortality rate, it offers a safe and effective means of cerebrospinal fluid diversion into a sterile compartment without loss of essential electrolytes. As more patients with treated hydrocephalus live longer, more abdominal complications of ventriculo-peritoneal shunts are being encountered. Abdominal signs and symptoms may develop acutely without appreciable neurological deterioration. The high morbidity associated with acute abdomen necessitates a quick and accurate diagnosis.

It has long been recognized that cerebrospinal fluid can collect and persist within the peritoneal cavity due to poor absorption in patients with a ventriculo-peritoneal shunt. Formation of a pseudocyst usually leads to either an acute abdomen or chronic abdominal distention. In this article, the clinical features of five patients with ventriculo-peritoneal shunts who developed acute abdominal symptoms, not related to pseudocysts, were analyzed. Diagnostic modalities and management alternatives are discussed.

## Case Presentation:

**Case One:** V.F.R. a 5 year old female patient with a right ventriculo-peritoneal shunt for congenital hydrocephalus and previous abdominal surgery for omphalocele, was admitted to the emergency room of the University Pediatric Hospital with a 24 hour history of severe right lower quadrant pain, abdominal distention, fever, nausea -vomiting and rebound tenderness. Abdominal sonogram did not reveal pseudocyst formation. KUB revealed air fluid levels and the CBC showed a moderate leukocytosis of 15,000. Cerebrospinal fluid removed from the shunt reservoir revealed no infection.

There was no shunt malfunction. Emergency abdominal surgery revealed a diffuse inflammatory reaction with fibrinoid material covering the peritoneal catheter. The distal (peritoneal) catheter was left inside the abdominal cavity. Intraoperative culture results were negative for infection and the patient was discharged home without symptoms, four days after the surgery. Review of the old record revealed an intraventricular hemorrhage 10 days prior to this admission during the revision of a proximal (ventricular) catheter malfunction. Blood products from the intraventricular hemorrhage may have been the cause of an aseptic abdominal peritonitis of acute onset.

**Case Two:** S.C. a 5 year old female patient with a congenital immunodeficiency syndrome and ventriculo-peritoneal shunt after meningitis was admitted to the University Pediatric Hospital with a 1 day history of acute abdominal pain, nausea and vomiting, and mild abdominal distention. X-rays revealed a partial small intestinal obstruction. Abdominal CT scan and sonogram were negative for masses or fluid collections. Cerebrospinal fluid cultures revealed an infection with *Pseudomonas aeruginosa*.

Upon removal of the shunt system, a thick collection of pus was found along the catheter's subcutaneous tract. An external ventricular drainage system was established, replacing the ventriculo-peritoneal shunt. Abdominal symptoms resolved completely within 24 hours. Intravenous antibiotic therapy was given and a ventriculo-peritoneal shunt was placed in the contralateral side of the abdomen, after appropriate sterilization of the cerebrospinal fluid. The patient was discharged, but readmitted 4 days later with the same symptoms. Exteriorization of the distal (peritoneal) catheter revealed pus at the entrance site of the catheter into the abdomen. Abdominal symptoms subsided the next day. After appropriate antibiotic therapy, a ventriculo-peritoneal shunt was placed on the contralateral side without any further complications.

**Case Three:** J.M.L. a 10 month old patient with a subtotal resection of a chiasmatic optic glioma and implantation of bilateral subduro-peritoneal shunts for subdural hygromas, two weeks prior to admission, was admitted to the University Pediatric Hospital with a 24 hour history of abdominal distention. Abdominal sonogram revealed a large fluid accumulation in the entire peritoneal cavity. Exteriorization of the distal (peritoneal) catheter resolved the acute abdominal symptoms. A ventriculo-atrial shunt was placed in view of the poor cerebrospinal fluid absorption in the peritoneal cavity. No evidence of infection was found.

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**Case Four:** C.R.M. a 4 year old male patient with a ventriculo-peritoneal shunt placed prior to the gross total resection of a large, solid cerebellar astrocytoma, developed acute right lower quadrant pain, nausea and vomiting, mild abdominal distention, and rebound tenderness 4 days after surgery. Abdominal manifestations abated after the exteriorization of the distal (peritoneal) catheter. Cerebrospinal fluid culture revealed *Staphylococcus epidermidis*. At this time, no evidence of cerebrospinal fluid obstruction was identified by CT scan. We then proceeded to remove completely the ventriculo-peritoneal shunt, since the obstruction to CSF flow was resolved by removal of the tumor.

**Case Five:** J.R.L. is an 11 month old infant with a ventriculo-peritoneal shunt infection with *E. coli*. Intravenous antibiotics were given for two weeks and the patient was sent home after repeated negative CSF cultures. The infant was readmitted to the University Pediatric Hospital 1 week later with abdominal distention and acute right upper quadrant tenderness around the area of the distal tip of the peritoneal shunt catheter. Exteriorization of the distal (peritoneal) catheter revealed a purulent peritoneal discharge from the entrance site of the catheter into the abdomen. Abdominal signs resolved in the next 24 hours. A ventriculo-atrial shunt was placed after sterilization of the cerebrospinal fluid with intravenous antibiotics.

## Discussion

A large head, an inherent characteristic of hydrocephalus in the young, has long interested physicians. The management of hydrocephalus is a fascinating study of technical innovation and clinical research. Establishing a communication between the cerebrospinal fluid pathways and the vascular system, suggested by Gartner in 1895, opened new avenues of clinical and technical investigation.

A major breakthrough in the treatment of hydrocephalus occurred when Holter, an engineer, invented a valve for the diversion of cerebrospinal fluid. Pudenz, et al; described a new technique (ventriculo-atriostomy) in 1957 for shunting cerebrospinal fluid into the right atrium of the heart.

Although effective and simple ventricular shunting into the atrium carries serious complications in a small percentage of cases. Complications include: obstruction, shunt nephritis, pulmonary embolus, perforation of the heart and endocarditis. It was not until 1967, that R.H. Ames reported the successful use of the abdominal cavity for cerebrospinal fluid diversion. This technique has become the treatment of choice for most hydrocephalic patients. In a small percentage of patients, it has created a new etiologic factor for acute abdomen.

Five patients with acute abdominal complaints were reviewed. Their ages ranged from 10 months to 5 years. Three patients were female and 2 were male. The etiology of the hydrocephalus varied considerably and had no correlation with the development of abdominal symptoms. Abdominal pain, nausea and vomiting, and decreased appetite were the most frequent symptoms.

On physical examination, all patients showed acute abdominal distention: bowel sounds were decreased in all patients, but were not absent. No palpable abdominal masses were felt in any patient. Early during the development of the acute abdominal symptoms, tenderness was localized to the side of the distal (peritoneal) catheter. As the condition progressed, tenderness became more diffuse. This contrasts with the classical pain of acute appendicitis, which is initially diffuse over the lower epigastrium and steadily localizes in the right lower quadrant.

Abdominal x-rays showed a pattern of partial intestinal obstruction in all cases, except in case 3, where ascitis was suggested. No pseudocyst was identified in radiological studies. Culture results from cerebrospinal fluid revealed infection in case 2 (*Pseudomonas aeruginosa*), case 4 (*Staphylococcus epidermidis*), and case 5 (*E. coli*). Most of the infections developed within 10 days from the latest proximal shunt revision. This suggests the idea that recent intraventricular complications might be one of the causes of acute abdominal symptoms in patients with ventriculo-peritoneal shunts.

Management included exteriorization of the distal (peritoneal) catheter in conjunction with systemic antibiotics, if there was documented infection. Cerebrospinal fluid diversion with a contralateral ventriculo-peritoneal shunt was effective in three cases, although atrial diversion was required in case number 3 because of peritoneal malabsorption. In case 5 a ventriculo-atrial shunt was performed arbitrarily.

## Conclusion

Acute abdominal manifestations in patients with ventriculo-peritoneal shunts requires urgent surgical and neurosurgical evaluation. When the abdominal signs and symptoms are clearly related to the shunt system, abdominal surgical exploration is unnecessary. Cerebrospinal fluid infection must be ruled out. Gram stain, cell count, and chemistries must be obtained immediately. A proximal (ventricular) catheter, or distal (peritoneal) catheter shunt malfunction can be diagnosed during cerebrospinal fluid collection.

For patients with distal (peritoneal) catheter complications, such as abdominal distention, peritonitis or shunt wound infection, exteriorization of the distal catheter appears to improve symptoms rapidly. Ten days of cerebrospinal fluid sterility while the patient is receiving antibiotics is required, before implantation of a new shunt system is attempted. Replacement with a contralateral distal (peritoneal) catheter into the abdominal cavity should be attempted, owing to the low morbidity associated with the ventriculo-peritoneal shunt procedure. If the absorptive capacity of the peritoneum has been impaired by the irritative process, an atrial catheter should be placed instead. The reason for the favorable response of these patients by simple removal of the peritoneal shunt, may be explained by the fact that the peritonitis is localized about the distal shunt and the removal of the peritoneal catheter removes an irritative focus.



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## RESPUESTAS

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|------|-------|
| 1) a | 7) a  |
| 2) e | 8) c  |
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# MEDICAL ASPECTS OF NUTRITION

## Update and review of anorexia nervosa\*

Alexander R. Lucas, MD\*\*

**A**norexia nervosa is an illness usually occurring in girls shortly after puberty or later in adolescence. It is characterized by self-imposed weight loss, amenorrhea and a distorted attitude toward eating and body weight. The disorder less often begins before the onset of menstruation or during adulthood. It rarely occurs in boys.<sup>1</sup>

Although medical descriptions of anorexia nervosa can be found dating from several centuries ago, the disease was considered rare until interest focused on it in recent decades. Frequent reports of the disorder and societal attention to dieting and slimming have led to the belief that the illness has become increasingly common.<sup>1</sup> There remains a controversy as to whether or not the underlying cause is a biological or psychological predisposition to anorexia nervosa. Treatment still poses many difficulties and several theories are supported. Long-term studies are beginning to provide insight about the etiology and outcome of the disorder.

### Causes

The specific cause of anorexia nervosa still is unknown but most scientific evidence suggest that there is an interaction of biological and psychosocial factors.<sup>2</sup> Recent evidence implicates a genetic predisposition with twin studies confirming a higher concordance rate among female identical (monozygotic) twins (56%) than among female fraternal (dizygotic) twins (7%).<sup>3</sup> It is well documented that there is a disturbance in the hypothalamic-anterior pituitary-gonadal axis.<sup>4</sup> Recent studies suggest that a central nervous system defect, if it exists, is above the level of the hypothalamus.<sup>5</sup> Most evidence, however, suggests that these disturbances are secondary to malnutrition.<sup>6</sup> Dieting appears to trigger a process of continu-

ing weight loss and hypometabolic adaptation in vulnerable individuals leading to a vicious cycle that becomes self-perpetuating.<sup>7</sup>

Another organ system that may play a role in predisposing individuals to develop anorexia nervosa is the gastrointestinal tract. History of eating disturbances in infancy and early childhood is not unusual and slow gastric emptying has been demonstrated in patients with anorexia nervosa. Undernutrition can cause such abnormalities but recent evidence points to the possibility that there are pre-existing irregularities in gastrointestinal motility that are not corrected with weight gain. These disturbances can set the stage for the illness by heightening patients' awareness of gastric fullness and discomfort.<sup>8</sup>

Pre-illness personality in anorexia nervosa varies considerably. However, the girl who develops the disorder typically is conscientious, intensely achievement oriented and perfectionistic. It has been suggested that there is a "neurotic perfectionism" associated with poor self-esteem, rather than effective perfectionism.<sup>9</sup> Family interactional patterns characterized by enmeshment or overinvolvement, overprotectiveness, rigidity and poor conflict resolution have been implicated.<sup>10</sup> However, a great variety of family dynamic patterns has been demonstrated in the families of children who develop anorexia nervosa. Some of the interactions described may be natural reactions to having a starving child in the family.<sup>11</sup> Social influences, expressed in the cultural obsession with thinness, undoubtedly have a powerful bearing on the development of the disorder. However, all teenage girls and young women are exposed to these pressures and most likely that such pressures, as well as characteristic psychological patterns, interact with biological vulnerability to result in the illness.

### Epidemiology

Anorexia nervosa occurs eight to twelve times more frequently in females than in males. Among females, more than half of the cases begin before age 20 years and about three-quarters occur before age 25 years. Fewer

\**Contemporary Nutrition*, Vol. 14, 1989. Reprinted with permission from General Mills, Inc. Minneapolis, Minnesota.

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than 10% have premenarchal onset. The 1985 prevalence in Rochester, Minnesota, was found to be 0.3% for females and 0.02% for males. However, among 15- to 19-year-old girls, the prevalence was 0.5%<sup>12</sup>

Estimates of the annual incidence in Western Europe and in the United States, based on hospitalized cases and psychiatric case registers, have shown an apparent increase from 0.5 per 100,000 in the 1980s.<sup>13</sup> The only population-based study covering a 50-year span showed a higher incidence rate of 8.2 per 100,000 ( $\uparrow$ 4.6 for females and 1.8 for males). This study showed no change in the rates for females age 20 years and older. Among the most susceptible group, females age 15 through 24 years, an increasing trend was found from 1935-84 with rates rising from 13.4 per 100,000 in 1935-39 to 76.1 per 100,000 in 1980-84.<sup>12</sup> Severe anorexia nervosa (emaciation with delusions about body image) still is relatively rare and the occurrence of this form of disorder may not have varied over time. Milder forms (lesser magnitudes of weight loss), especially those occurring in teenage girls and young adult women, have been on the increase in recent decades.

### Behavioral Characteristics

The diagnosis of anorexia nervosa depends on the presence of three characteristics:

- Marked weight loss that is self-induced.
- A specific psychopathology characterized by avoidance of fatness.
- Endocrine changes manifested by amenorrhea in females and loss of sexual interest and potency in males.

In premenarchal anorexia nervosa, there need not be actual weight loss but failure to gain during the phase of active growth.<sup>14</sup> The endocrine disorder then results in delay of pubertal development and of growth. Atypical or partial forms of anorexia nervosa are common in individuals who do not meet all of the criteria.

The disorder begins after puberty in a girl whose growth and development have previously been normal. Often these girls have shown no signs of serious disturbance beforehand and parents may comment that the affected daughter has been the best adjusted of their children. Typically, the girls have been highly conforming, ambitious and achievement oriented. They have high standards for their own behavior, are fearful of making others angry and are afraid of criticism.<sup>15</sup>

The history of one with anorexia nervosa is that of progressive self-starvation which may begin with apparently normal concern about dieting. Food restriction becomes more and more stringent and is accompanied by increasing exercise. Pubertal changes in body shape may give rise to concerns about body image. These concerns become exaggerated and unrealistic. As focus on idiosyncratic eating habits and weight loss becomes an all-consuming obsession, social withdrawal and alienation from family members results. While increased activity and productivity accompany the early stages of the illness, symptoms of depression ensue. Often the individual with anorexia nervosa will deny that anything is wrong and resist medical examination and treatment.<sup>15</sup>

### Medical Complications

A wide range of complications, including any of the consequences of starvation, is possible in anorexia nervosa. This disorder may result in delays in pubertal and sexual development. A delay in emotional development is equally important. Fat depletion is the most noticeable physical consequence. This is to a large measure compensated for by hypometabolic adaptation. When caloric restriction is uncomplicated by qualitative deficiencies in the diet, serious complications may be forestalled. Qualitative deficiencies in the diet may lead to anemia, hypoproteinemia and less commonly to vitamin deficiencies. Gastrointestinal complications, including decreased motility and atonic gut, may occur. Prolonged reduction in estrogen levels, as heralded by amenorrhea, leads to osteoporosis even in young individuals with anorexia nervosa.<sup>18</sup> Serious electrolyte imbalances, notably hypokalemia (reduced blood potassium levels) can occur when vomiting, laxative or diuretic abuse are practiced. Muscular weakness, cardiac arrhythmias and renal impairment may occur. These complications can lead to chronic cardiac and renal damage or to sudden death.<sup>16</sup>

The most significant complication is chronicity. Many individuals, particularly those with mild forms of anorexia nervosa recover completely without subsequent complications. Some recover after many years of illness. About 15% to 30%, however, remain chronically ill.<sup>17</sup> Some of the chronically ill patients with anorexia nervosa develop bulimia nervosa, characterized by episodic binge eating, vomiting and purging.<sup>18</sup> Death from the disorder may occur relatively early from electrolyte disturbance or it may be a late outcome due to chronic starvation.

### Treatment

Theories surrounding treatment have focused on physical aspects by restoring weight or on using psychological means to deal with personal or interpersonal conflicts. Those who believe that the illness develops within the context of family interactions have focused on family therapy. While each of these methods has merit in treating certain individuals, there is now consensus that most patients require a multidimensional approach that addresses both the physiological and psychological manifestations of the illness.<sup>15</sup>

Resumption of normal eating patterns is a goal of treatment that leads to weight restoration. There is controversy about how rapidly weight should be restored. Some experts advocate a behavioral paradigm requiring rapid weight gain, while others recommend a gradual increase in the quantities of food consumed with slower weight gain, as a more physiologically and psychologically acceptable approach.<sup>19</sup> As yet, no studies have attempted to compare these approaches to determine which method is ultimately more effective. However, the younger the patient, the more important it is to involve the family in treatment.<sup>15</sup> With numerous hospital-based programs that have developed in recent years, there is a tendency to rush patients to a hospital even when the disorder is relatively mild. Outpatient

treatment is preferred for most. It has the advantage of maintaining the patient in her own environment and in involving her in her own therapy so that she learns to make changes in her life-style that led to health. If the illness is severe and family and environmental circumstances are too damaging or if there is failure to respond to outpatient treatment, then hospitalization is indicated.

### Summary

Anorexia nervosa is not a new disease but it has become increasingly recognized and occurs more frequently in adolescent girls and young women. Among older women, its incidence has remained constant. Scientific evidence suggests that dieting triggers a process of catastrophic weight loss in persons who are psychologically and physiologically vulnerable. Long-term studies are demonstrating diverse outcomes ranging from full recovery to chronicity and death. Treatment is often based on unproven theory and on short-term goals. Research studies comparing the effects of different treatment regimens are needed.

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## AMERICAN ACADEMY OF PEDIATRICS

### HEALTHY DIETS ATTAINABLE FOR CHILDREN

Lower cholesterol and fat intakes are attainable within the current eating patterns of healthy children and adolescents, according to a recent study. The report also notes that in the children studied, current fat intake was similar to the national average which has been decreasing over the last few years.

Published in the October issue of *Pediatrics*, the journal of the American Academy of Pediatrics (AAP), the study of 138 children and adolescents finds that a substantial portion of them consumed diets low in fat and cholesterol with foods they chose themselves.

The authors note that there did not appear to be any differences in the intake of other vitamins and minerals among students eating low fat diets compared with those eating high fat diets.

The study, from the University of Texas Health Science Center School of Public Health, Houston, analyzed the nutrient intake and food patterns among fifth to twelfth grade students in The Woodlands, a suburban community in Texas, during 1988.

The data indicates that among the students:

- 34 percent consumed more than 38 percent of calories from fat,
- 7 percent consumed less than 10 percent of calories from saturated fat;
- and more than 97 percent ate less than 300 milligrams of cholesterol per day.

"It is not unreasonable to hypothesize that the public message concerning the consumption of lower fat diets has had some effect on the food consumption patterns of these children and adolescents," the authors write.

"Current dietary recommendations about fat intake are achievable and acceptable within the range of intakes

seen in this population of healthy children and adolescents," the authors add.\*

The data do not support the belief that children consuming a diet with less than 30 percent total fat and less than 10 percent saturated fat is an unusual or unattainable dietary pattern, the authors note.

On the other hand, the data also show that there is still a large percentage of school-aged children eating diets with high levels of saturated fat. The authors stress that there is a need for dietary intervention and programs for children that will attempt to prevent the rise in cholesterol levels between childhood and adulthood.

*\*The American Heart Association, the National Institutes of Health Consensus Development Panel, and the American Academy of Pediatrics have recommended dietary modifications for all Americans older than 2 years of age. The first two groups recommend a diet that contains less than 30 percent of calories from total fat, less than 10 percent from saturated fat, and no more than 10 percent from polyunsaturated fat. The American Academy of Pediatrics recommends a range of fat intake from 30 - 40 percent, suggesting that the lower end of this range would be preferable.*

### FAMILY VIOLENCE: WHAT WE KNOW AND CAN DO

Violence between family members is more common than violence in any other setting or between any other individuals, a sociologist said today.

According to Richard Gelles, Ph.D., Director of the Family Violence Research Program at the University of Rhode Island, Kingston, criminals and assassins account for only half of all homicides in the U.S.; 20 percent of the other half of homicides occur between family members. The problem of family violence affects some 8 to 10 million American families in the United States.

Dr. Gelles, who spoke at the American Academy of Pediatrics' (AAP) Annual Meeting, said family violence is far more extensive than any official statistics have indicated, yet even his own estimates are likely to be underestimated because they are based on what people are willing to reveal in a 60-minute interview.

"Poor families, black and hispanic families, non-English speaking families, and socially-marginal families are disproportionately susceptible to having the label 'abuse' attached to behavior in their households," Dr. Gelles stated. Mainstream families, well-to-do families, and families of professionals and academics find that injuries to their children are frequently classified as accidents.

According to Dr. Gelles, there are four factors generally related to family violence:

- \* an abused child's chances of becoming an abusive adult are, in some instances, a thousand times greater than a non-abused child. But children who are

abused will not always grow up to be abusers themselves.

- \* abuse of all kinds is more likely to occur in lower socioeconomic families
- \* abusive families are more isolated — they belong to few community organizations, have little contact with neighbors, relatives and families, and move often
- \* the higher the social stress, the greater the chance that the family will be abusive.

Dr. Gelles added that the consequences of violence for women and children, beyond the obvious physical injuries, also involve psychological distress and suicide attempts for women, and school, behavior and delinquency problems for children.

"People abuse family members because they can," Dr. Gelles noted. "There are rewards to be gained from being abusive including the immediate reward of getting someone to stop doing something, of inflicting pain on someone as revenge, of controlling behavior, and especially power."

The rewards for this behavior are higher than the costs, Dr. Gelles stated. The private nature of the family unit, the reluctance of social institutions and agencies to intervene, and the low potential for intervention for offenders reduce the costs of abuse and violence. The cultural approval of violence and the ability to control victims are significant rewards for violent behaviors in families.

Dr. Gelles recommended that a child's full medical, psychological and sociological information be examined in order to diagnose how an injury occurred and whether it was accidental or inflicted.

#### **SLEEP DISORDERS IN CHILDREN: A COMMON CONCERN FOR MANY PARENTS**

Significant sleep disorders affect over 25 percent of children and provide the basis for some of the most common questions parents ask their pediatricians, an expert said today.

Richard Ferber, MD, speaking at the American Academy of Pediatrics (AAP) Annual Meeting said that bedtime difficulties, nap problems, nighttime fears, sleepwalking, bedwetting and sleep terrors are problems many children face.

Dr. Ferber, Director, Center for Pediatric Sleep Disorders, Children's Hospital, and Assistant Professor of Neurology, Harvard Medical School, Boston, said that the significance of certain events occurring in sleep varies depending on the age of the child and/or frequency of occurrence of the events.

For example, nighttime wetting and daytime napping are "normal" in infants and toddlers but "abnormal" by middle childhood. Similarly, occasional sleep terrors, sleepwalking, or headbanging may be normal development events in the young child but abnormal when particularly intense, frequent, or long lasting, or when they occur in the older child.

Sleep disorders must be classified according to the child's age, development level, and the specific pattern of symptoms. Parents or other caretakers usually provide the history of a child's sleep disorder, therefore it is their complaint, not the child's that must be evaluated, according to Dr. Ferber. Parent's complaints are often about the effect the child's sleep problem is having on their lives and the problem often lies in the interaction between the parent and child.

"The child may have no complaint and may be happy sleeping in his parents' bed, staying up late or waking early in the morning," Dr. Ferber noted.

Children often experience sleeplessness—they may not want to sleep and try to stay awake. Sleeplessness may occur as a result of anxieties, stress, colic, chronic illness, medication effects, and environmental and interactional problems such as excessive nighttime feeding, poor limit-setting and inappropriate sleep associations.

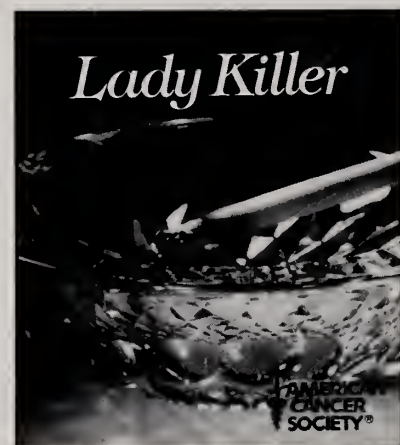
If a child is experiencing symptoms of sleeplessness and/or sleepiness it may be because of sleep-wake schedule problems resulting from an early bedtime, an irregular bedtime schedule or no schedule at all.

"It is important to keep in mind that symptoms of sleepiness in children are not always obvious," Dr. Ferber said. Sleepy children do not necessarily yawn, complain of being sleepy, or even nap—instead they may appear overactive, impulsive, distractible, and irritable with attentional difficulties and tantrums.

Some sleep disorders such as narcolepsy and bedwetting, are more common in children whose parents suffer or suffered from the same disorder.

"In the initial assessment of a child's sleep disorder, certain areas should be considered," Dr. Ferber stated. "These include a detailed sleep history, a general medical history, a complete social history, an assessment of the child's psychological/developmental status and a physical examination."

"Children develop sleep problems quickly. The other side of the coin, however, is that unlike an adult they respond quickly to intervention," Dr. Ferber concluded. A sleepless child can often be helped to sleep through the night within only a few days. And in most cases this means correcting habits and changing schedules, not using medications.







## ASTHMA HOSPITALIZATIONS, DEATHS RISING AMONG YOUNG CHILDREN

Asthma morbidity and mortality rates appear to be on the rise, conclude two studies in the *Journal of the American Medical Association*.

Previous research has suggested that the increase in reported asthma cases and deaths may have been due to a change in disease coding procedures which took effect in 1979. But the *JAMA* studies now say the increase may be real, especially among poor, black youth.

Peter J. Gergen, MD, MPH, of the National Center for Health Statistics, Hyattsville, Md., and Kevin B. Weiss, MD, MPH, of George Washington University Medical Center, Washington, D.C., reviewed national trends in asthma hospitalizations from 1979 through 1987. They analyzed data from the National Hospital Discharge Survey, an annual study of hospitalizations, diagnoses and payment methods.

Asthma hospitalizations among children aged 17 years and younger increased 4.5 percent per year during the study period. The largest per annum increase (5.0 percent) occurred among children aged 0 to 4 years, while the smallest (2.9 percent per year) occurred among 5 to 17 year olds.

Young black children showed the largest increase in asthma hospitalizations, the authors report. Among children aged 0 to 4 years, blacks had approximately 1.8 times the increase of whites. In 1979, the hospitalization rate was 2.67 and 5.76 per 1,000 population for whites and blacks, respectively; by 1987, the rate had increased to 3.53 for whites and 10.16 for blacks. Medicaid paid a larger portion of hospital costs for children under age 4, suggesting that asthmatic children from low income families suffer most.

The researchers then looked at possible reasons for the rate increase. They found, however, that the total number of hospitalizations for children and admission rates for children with lower respiratory disease had declined over the years studied. Hospitalizations for bronchial conditions also generally decreased, they report.

"It is clear from these results that childhood asthma hospitalization rates are increasing," the authors conclude. Physicians may be diagnosing more wheezing illnesses in children as asthma rather than bronchitis,

they say. Environmental pollution, including maternal smoking, may also play a role. "Poverty may be a surrogate measure for many things that could increase asthma hospitalization rates, for example, lack of access to care," write the authors.

In a related *JAMA* study, Weiss and coauthor, Diane K. Wagener, PhD, of the National Center for Health Statistics, examined deaths from asthma in the U.S. from 1968 through 1987. Asthma mortality in persons aged 5 to 34 years declined steadily from 1968 to 1977, but increased dramatically from 1978 through 1987. The mortality rate increased significantly faster among the 5 to 15 year olds than in those aged 15 to 34 years.

The increase in mortality rates could not be attributed to the diagnostic coding change since the rise began in 1978, a year before the change took effect.

Substantial differences were found in mortality rates between the races, with higher rates for nonwhites than whites. "In 1987, the highest rate was that among non-white males, 13.5 deaths per million of population—nearly five times as high as the rate among whites of both sexes," the authors say.

When the authors studied specific geographic regions, four areas were found to have asthma mortality rates which were higher than that of the general U.S. population: New York City; Cook County, Ill.; Maricopa County, Ariz.; and Fresno County, Calif. When combined, New York and Cook County accounted for 21.1 percent of all asthma deaths in this age group, suggesting these two areas "are driving the U.S. trend" in rising asthma mortality, they say.

A "higher prevalence of asthma, changing patterns of disease severity, and changing patterns of medical care" may be responsible for the upward trend, the researchers say. "However, whatever the reason for the increase, both asthma mortality and hospitalization continue to affect nonwhites, urban areas, and the poor disproportionately," they conclude.

"The contribution of health care access, availability, and utilization to the increase in asthma morbidity and mortality is a fascinating question for which few answers are available," write A. Sonia Buist, MD, of the Oregon Health Sciences University, Portland, and William M. Vollmer, PhD, of Kaiser Permanente Center for Health Research, Portland, in their accompanying editorial.

The upward trends "are worrisome, because they come at a time when morbidity and mortality from many chronic diseases are decreasing, when we think we have a fairly sound understanding of the pathophysiology of asthma, and when we believe we have more effective drugs for its management," the authors say.

"How much of this increase is real and how much is related to the problems of diagnosis and classification is not clear," write the authors. "Physicians need to be on the lookout for the undiagnosed asthmatic and for the brittle asthmatic who is at particular risk for fatal asthma," they say.

*JAMA* October 3, 1990



## BOLETIN DE LA ASOCIACION MEDICA PUERTO RICO

# AGRADECIMIENTO A COLABORADORES

La Junta Editora del Boletín de la Asociación Médica de Puerto Rico reconoce la cooperación y apoyo brindado por una serie de personas para lograr la misión editorial recomendada.

Pocos de nuestros lectores y autores conocen la enorme contribución que hacen los arbitros al proceso de publicación de artículos en el Boletín. Estas personas desinteresadamente brindan su esfuerzo y su tiempo al análisis y corrección de los manuscritos sometidos para evaluación por esta Junta. También brindan valiosos servicios al Boletín con comentarios editoriales, artículos de repaso, material gráfico y otras tareas solicitadas por la Junta Editora para lograr confeccionar una publicación científica de calidad. Aprovechamos esta ocasión para expresar públicamente a estas personas nuestro agradecimiento por su valiosa labor durante todo este año.

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# VASOTEC<sup>®</sup>

(ENALAPRIL MALEATE) MSD

VASOTEC is available in 2.5-mg, 5-mg, 10-mg, and 20-mg tablet strengths.

**Contraindications:** VASOTEC<sup>®</sup> (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

**Warnings:** **Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

**Hypotension:** Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Patients with heart failure given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy. (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hypotension, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in patients with heart failure) reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

**Neutropenia/Agranulocytosis:** Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

**Precautions:** **General:** **Impaired Renal Function.** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

**Evaluation of patients with hypertension or heart failure should always include assessment of renal function.** (See DOSAGE AND ADMINISTRATION.)

**Hyperkalemia:** Elevated serum potassium (>5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See Drug Interactions.)

**Surgery/Anesthesia:** In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

#### Information for Patients:

**Angioedema:** Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

**Hypotension:** Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

**Hyperkalemia:** Patients should be told not to use salt substitutes containing potassium without consulting their physician.

**Neutropenia:** Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

**NOTE:** As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

#### Drug Interactions:

**Hypotension: Patients on Diuretic Therapy:** Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

**Agents Causing Renin Release:** The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

**Other Cardiovascular Agents:** VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyl-dopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

**Agents Increasing Serum Potassium:** VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, furosemide, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

**Lithium:** Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

**Pregnancy—Category C:** There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters. There are no adequate and well-controlled studies of enalapril in pregnant women. However, data are available that show enalapril crosses the human placenta. Because the risk of fetal toxicity with the use of ACE inhibitors has not

been clearly defined, VASOTEC<sup>®</sup> (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome. Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality.

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypotension, or the underlying prematurity.

**Nursing Mothers:** Milk in lactating rats contains radioactivity following administration of <sup>14</sup>C enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

**Pediatric Use:** Safety and effectiveness in children have not been established.

**Adverse Reactions:** VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

**HYPERTENSION:** The most frequent clinical adverse experiences in controlled trials were: headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

**HEART FAILURE:** The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

**Cardiovascular:** Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, Hypotension); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances; atrial fibrillation; palpitation.

**Digestive:** Ileus, pancreatitis, hepatitis (hepatocellular or cholestatic jaundice), melena, anorexia, dyspepsia, constipation, glossitis, stomatitis, dry mouth.

**Musculoskeletal:** Muscle cramps.

**Nervous/Psychiatric:** Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

**Urogenital:** Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

**Respiratory:** Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection.

**Skin:** Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pruritus, alopecia, flushing, hyperhidrosis.

**Special Senses:** Blurred vision, taste alteration, anosmia, tinnitus, conjunctivitis, dry eyes, tearing.

A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash, and other dermatologic manifestations.

**Angioedema:** Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately (see WARNINGS.)

**Hypotension:** In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

#### Clinical Laboratory Test Findings

**Serum Electrolytes:** Hyperkalemia (see PRECAUTIONS), hyponatremia.

**Creatinine, Blood Urea Nitrogen:** In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 1% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

**Hemoglobin and Hematocrit:** Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.5 and 1.0 vol %, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

**Other (Causal Relationship Unknown):** In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported. A few cases of hemolysis have been reported in patients with G6PD deficiency.

**Liver Function Tests:** Elevations of liver enzymes and/or serum bilirubin have occurred.

**Dosage and Administration:** **Hypertension:** In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.)

The recommended initial dose in patients on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

**Dosage Adjustment in Hypertensive Patients with Renal Impairment:** The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

**Heart Failure:** VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with once-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects.) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

**Dosage Adjustment in Patients with Heart Failure and Renal Impairment or Hyponatremia:** In patients with heart failure who have hyponatremia (serum sodium < 130 mEq/L) or with serum creatinine > 1 mg/dL, therapy should be initiated with 2.5 mg once daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, Heart Failure, WARNINGS, and PRECAUTIONS, Drug Interactions.) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

For more detailed information, consult your MSD Representative or see Prescribing Information, Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19386.

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VASOTEC is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor. For a Brief Summary of Prescribing Information, please see the last page of this advertisement

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